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Report to Congressional Requesters

March 2020

FDA DRUG APPROVAL

Application Review Times Largely Reflect Agency Goals

Accessible Version

GAO-20-244

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GAO Highlights

Highlights of GAO-20-244, a report to congressional requesters

Why GAO Did This Study

Before a drug can be marketed in the United States, FDA must determine that the drug is safe and effective for its intended use through a review of evidence that a drug sponsor—the entity seeking to market the drug—submits in an NDA. The review is conducted by one of FDA's divisions (17, at the time of GAO's review) that each specialize in a specific group of drug products, such as hematology products. NDA reviews are complex, and may involve not only an initial review, but also reviews of resubmissions if the initial review does not result in approval. Under FDA's PDUFA commitments, FDA's goal is to complete reviews of 90 percent of NDAs within specific time frames linked to key features of the NDAs.

GAO was asked to examine NDA review times across FDA's divisions. In this report, GAO examines (among other things) differences between FDA divisions in the key features of the NDAs they review and initial review times, as well as the extent to which key NDA features contribute to these differences.

GAO analyzed data from FDA's Center for Drug Evaluation and Research regarding 637 NDAs submitted from fiscal years 2014 through 2018. These data also included biologic license applications submitted to the center. GAO excluded NDAs that were withdrawn by the applicant before FDA completed a review, as well as NDAs for which FDA had not completed a review by March 31, 2019. GAO also interviewed FDA officials about the agency's review process and these review times.

The Department of Health and Human Services provided technical comments on a draft of this report, which GAO incorporated as appropriate.

View GAO-20-244. For more information, contact John Dicken at (202) 512-7114 or dickenj@gao.gov.

What GAO Found

Four key features of new drug applications (NDA) are linked to the time the Food and Drug Administration (FDA) takes to complete initial reviews of NDAs. Three key NDA features determine the time frames for initial review that would meet FDA's goals under the Prescription Drug User Fee Act (PDUFA) and its reauthorizations, which authorize FDA to collect user fees from drug sponsors:

- Whether or not the NDA qualifies for the priority review program, which is generally an expedited program for drugs that provide significant therapeutic improvements in the prevention, diagnosis, or treatment of a serious condition when compared to available drugs. The PDUFA goal for review of a priority NDA is 4 months less than for an otherwise similar standard NDA, for which the goal is to complete the review in 10 months.
- Whether or not the NDA involves a new molecular entity (an active ingredient that has not been previously marketed or approved in the United States). The PDUFA goal for review of an NDA with a new molecular entity is 2 months longer than for an NDA without one.
- Whether or not the applicant submits a major amendment (additional or new information, such as a major new clinical study) while the NDA is under review. The PDUFA goal for a review of an NDA may be extended by 3 months if the applicant submits a major amendment.

The fourth key NDA feature is whether or not it qualified for one or more of three other expedited programs for drugs intended to treat serious or life-threatening conditions.

GAO's analysis of 637 NDAs submitted from fiscal years 2014 through 2018 indicated that the proportion of NDAs with these key features differed among FDA review divisions. For example, 6 percent of the NDAs reviewed by the dermatology and dental division had a priority designation, compared to 56 percent for the anti-infective division. FDA has reported that some divisions, such as the oncology divisions, generally regulate products for conditions that are more likely to be serious or life-threatening, and, therefore, those products may be more likely to qualify for priority designation and other expedited programs.

GAO found that FDA's divisions differed in the average number of days they took to complete an initial review of NDAs, and these differences largely reflected the key features of the NDAs they reviewed. GAO's analysis shows that the time FDA took to complete an initial review of NDAs was affected by (1) the target time frame for completion of the review under the agency's PDUFA goals, (2) the number of expedited programs for which the NDA qualified, and (3) the division performing the review. GAO also found that the target time frame for review was largely responsible for differences in initial review times. Specifically, NDAs with key features that resulted in shorter target time frames for review under FDA's PDUFA goals had shorter initial review times. Controlling for the effects of these target time frames and the number of expedited programs for which the NDA qualified, GAO found that most of the divisions' average review times were similar to (within 2 weeks of) each other.

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Abbreviations

BLA	biologic license application
CDER	Center for Drug Evaluation and Research
Cures Act	21st Century Cures Act
FDA	Food and Drug Administration
NDA	new drug application
PDUFA	Prescription Drug User Fee Act

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U.S. GOVERNMENT ACCOUNTABILITY OFFICE
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March 6, 2020

The Honorable Michael B. Enzi
Chairman
Subcommittee on Primary Health and Retirement Security
Committee on Health, Education, Labor & Pensions
United States Senate

The Honorable Richard Burr
United States Senate

The Honorable Pat Roberts
United States Senate

Getting safe, effective drugs to market in the United States typically involves a lengthy drug development process. Before the drug can be marketed, the Food and Drug Administration (FDA), an agency within the Department Health and Human Services, must determine that the drug is safe and effective for its intended use through a review of evidence that a drug sponsor submits in a new drug application (NDA).[1] The review is conducted by one of the agency's Center for Drug Evaluation and Research (CDER) divisions, each of which specialize in a specific group of drug products, such as hematology or neurology.[2]

Four key features of NDAs are linked to drug development and review processes. FDA's goal for completing its initial review of certain standard NDAs is 10 months after initial receipt, but some NDAs are subject to a

[1]A drug sponsor is the person or entity that assumes responsibility for marketing a new drug, including responsibility for complying with applicable laws and regulations. Drugs are chemically synthesized, while biological products—which include vaccines, blood products, and proteins, among other things—are derived from living sources such as humans, animals, and microorganisms. Unless otherwise indicated, we use the term "drug" in this report to refer to both chemically synthesized drugs and biological products. Some applications for the approval of biological products—biologic license applications (BLA)—are reviewed by FDA's Center for Biologics Evaluation and Research, while others are reviewed by FDA's Center for Drug Evaluation and Research (CDER). We included only the BLAs reviewed by CDER and we refer to all of CDER's NDAs and BLAs as NDAs.

[2]In September 2019, FDA announced that the agency received Congressional approval to reorganize CDER's Office of New Drugs, which had included 17 review divisions through most of the time covered by the work in this report. After the reorganization is fully implemented, there will be 27 clinical review divisions in the Office of New Drugs.

different initial review goal based on each of three key features of the NDA:

- FDA may designate NDAs for priority review when they are for drugs that provide a significant improvement in safety or effectiveness for treatment of a serious condition when compared to available drugs; FDA's goal is to review priority NDAs more rapidly than standard ones.
- FDA's goal includes extra time if the NDA involves a new molecular entity—an active ingredient that has not been previously marketed or approved for use in the United States.
- FDA may extend its goal if the applicant submits substantial additional information while the NDA is under review.

A fourth key feature of NDAs is whether they qualify for one or more of FDA's expedited programs, which are intended to help reduce the development or review time needed to bring a drug to market. NDAs for therapies intended to treat serious or life-threatening conditions may qualify for one or more of these programs.

NDA reviews are complex and may take multiple review cycles. While conducting its initial review, FDA may determine that it needs additional information or further evidence, and in such cases, the agency can end the initial review with a letter to the applicant describing specific deficiencies. The applicant can respond in a resubmission, initiating a new cycle of review.

Because drug sponsors must collect evidence to demonstrate the safety and effectiveness of new drugs, and these efforts represent a major component of drug development time and cost, the amount and nature of the evidence needed can be an important determinant of when and whether new therapies become available to the public. The issue of what constitutes sufficient evidence to support NDAs has been debated by FDA, the scientific community, industry, and others. FDA has typically required NDAs to include safety and effectiveness evidence for new drugs from two adequate and well-controlled clinical trials. However, under certain circumstances, drug sponsors can use different sources of evidence to show that a new drug is safe and effective for its intended use. The 21st Century Cures Act (Cures Act), enacted in 2016, directed FDA to evaluate and facilitate the use of these different sources of

evidence by FDA reviewers and drug sponsors to inform the agency's assessment of drug safety and effectiveness.[3]

FDA has published evidence showing that review times differ between divisions.[4] In light of this evidence, you asked us to examine NDA review times across FDA's divisions, as well as FDA's use of certain tools to inform the agency's assessment of drug safety and effectiveness. This report examines

1. differences between FDA divisions in the proportion of NDAs they review with key features;
2. differences between FDA divisions in the time taken to complete initial reviews and the extent to which the key NDA features contribute to these differences; and
3. actions FDA has recently taken to evaluate and facilitate the use of different sources of evidence to support NDAs.

To address our first two objectives, we analyzed data from FDA regarding 637 NDAs—the NDAs that were initially submitted from fiscal years 2014 through 2018.[5] (Appendix I provides a detailed description of the methodologies we used to analyze these data.) Our examination excluded NDAs that were withdrawn by the applicant before FDA completed an initial review, as well as NDAs for which FDA had not completed a review by March 31, 2019. For some analyses, we also excluded five NDAs, as described in appendix I, bringing the count of NDAs to 632. We reviewed the reliability of the data by conducting a series of electronic and logic tests to identify missing data or other anomalies and worked with FDA to correct information when we identified discrepancies. We determined that the data were sufficiently reliable for our purposes. In addition, although our focus was on initial review times, we also collected information about total review times—review times across all completed cycles of review; appendix II includes information

[3]Pub. L. No. 114-255, 130 Stat. 1033 (2016).

[4]A. Schick, K. L. Miller, M. Lanthier, and J. Woodcock, "What drives differences in review times among CDER divisions?" *Nature Reviews Drug Discovery*, vol. 14 (2015): p. 670.

[5]Fiscal year 2018 was the most recent year for which complete data were available at the time of our review. During the time period for which we obtained data, CDER had 17 review divisions, including two oncology divisions; FDA combined the NDAs for those two divisions in the data it provided.

about these total review times. Finally, we interviewed FDA officials about the agency's review process and these review times.

To examine recent FDA actions to evaluate and facilitate the use of different sources of evidence to support NDAs, we identified initiatives FDA started implementing as a result of the enactment of the Cures Act in late 2016. We focused our analysis on initiatives that (1) involve NDAs reviewed by CDER divisions and (2) could affect a variety of diseases and populations. We spoke with FDA officials and reviewed FDA documentation to learn about the initiatives and determine steps FDA has taken to implement the initiatives. We also interviewed two stakeholder groups (Pharmaceutical Research and Manufacturers of America and Biotechnology Innovation Organization) that represent drug sponsors about the initiatives.

We conducted this performance audit from July 2018 to February 2020 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

In 1992, the Prescription Drug User Fee Act (PDUFA) was enacted, in part, to provide additional funds for FDA to support the process of reviewing NDAs.[6] PDUFA authorized FDA to collect user fees from drug sponsors to supplement its annual appropriation for salaries and expenses.[7] PDUFA has been reauthorized every 5 years since 1992; most recently PDUFA VI reauthorized the prescription drug user fee program from fiscal year 2018 through fiscal year 2022.[8] As part of each

[6]Federal Food, Drug, and Cosmetic Act Amendments, Pub. L. No. 102-571, tit. I, 106 Stat. 4491, 4491-4500 (1992).

[7]User fees are fees assessed to users for goods and services provided by the federal government. Prescription drug user fees are collected and available for obligation only to the extent and in the amount provided in advance in appropriation acts.

[8]Food and Drug Administration Reauthorization Act of 2017, Pub. L. No. 115-52, tit. I, 131 Stat. 1005, 1006-1013 (2017).

reauthorization process, FDA identifies goals in a commitment letter to Congress. In general, these goals identify a percentage of certain types of applications that FDA is expected to review within specified time frames, including goals for the time the agency takes to complete reviews of different types of NDAs upon initial submission and resubmission.[9] For example, in its commitment letters for PDUFA V and VI, FDA committed to completing its initial review of 90 percent of priority NDAs that involve previously marketed or approved active ingredients within 6 months of receipt.[10]

As previously noted, four key features of NDAs are linked to drug development and review processes. For initial NDA reviews, the time frames for FDA's review that would meet its PDUFA V and VI commitments—its PDUFA goals—vary and are linked to three key features of the NDA.[11] (See table 1.) The target time frame for the initial review of any specific NDA under these user fee commitments reflects the goals associated with all three of the key features.

[9]The goals in the PDUFA commitment letters are the product of FDA's discussions with the regulated industry and public stakeholders.

[10]Under FDA's PDUFA V and VI commitment letters (which were the commitments in effect during the years for which we obtained data), FDA's goal is to review and act on 90 percent of such applications within that time frame. We refer to acting on a review as completing the review. See FDA, *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017*, accessed Nov. 5, 2019, https://www.fda.gov/media/81306/download; FDA, *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022*, accessed Nov. 5, 2019, https://www.fda.gov/media/99140/download.

[11]Under FDA's PDUFA goals, BLAs are treated like NDAs involving a new molecular entity and, like those NDAs, may receive a priority review designation and may be the subject of a major amendment.

Table 1: Key New Drug Application (NDA) Features Linked to FDA's Time Frames for Initial Review under Its Prescription Drug User Fee Act (PDUFA) V and VI Goals

Feature	Description	Time frame for review
Whether or not the NDA receives a priority review designation	An NDA can receive a priority review designation if the product would provide significant therapeutic improvements in the safety and effectiveness of the prevention, diagnosis, or treatment of a serious condition when compared to available drugs. Otherwise, it receives a standard review designation.[a]	4 months less for priority NDAs than for standard NDAs[b]
Whether or not the NDA involves a new molecular entity	A new molecular entity is generally an active ingredient that contains no active moieties that have been previously approved by FDA or have been previously marketed as a drug in the United States. Active moieties are certain molecules or ions responsible for the physiological or pharmacological action of the drug.	2 months more when a new molecular entity is involved than when no new molecular entities are involved[c]
Whether or not the applicant submitted a major amendment	A major amendment to a pending NDA (one under FDA review) is a submission of additional information that may include a major new clinical safety or efficacy study report or major new analyses of studies, among other things.	3 months more when the applicant submits a major amendment than when the applicant does not[d]

Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-20-244

Note: FDA's time frames for initial review reflect the time frames specified in FDA's goals in commitment letters associated with the PDUFA reauthorizations for fiscal years 2013 through 2017 (PDUFA V) and fiscal years 2018 through 2022 (PDUFA VI). Through these agreements, FDA has committed to reviewing and acting upon 90 percent of NDAs within the specified time frames. Under FDA's PDUFA goals, biologic license applications (BLA) are treated like NDAs involving a new molecular entity and, like those NDAs, may receive a priority review designation and may be the subject of a major amendment.

[a]A small number of NDAs receive priority review designation because the applicant uses a priority review voucher. FDA awards priority review vouchers to drug sponsors that develop and receive approval for certain products for tropical diseases, rare pediatric diseases, and medical countermeasures. A priority review voucher entitles the voucher holder to receive a 6-month priority review, rather than the typical 10-month standard review, for a future drug application for a drug to treat any disease or condition. Seven priority review vouchers were redeemed for NDAs reviewed by FDA's Center for Drug Evaluation and Research in fiscal years 2014 through 2018.

[b]The PDUFA goal is to review and act on standard NDAs that do not involve a new molecular entity within 10 months of FDA's receipt of the NDA. Priority review reduces this time to within 6 months of receipt. In addition, under its PDUFA VI commitment letter, FDA seeks to review certain NDAs that qualify for priority review, have the potential to meet an important public health need, and are likely to receive approval upon completion of the initial review, among other things, a least one month before the otherwise specified PDUFA goal.

[c]The PDUFA goal is to review and act on standard NDAs that involve a new molecular entity within 10 months following a 60 calendar day filing review period that begins on the date of FDA's receipt of the NDA (so the goal is a total of 12 months from receipt). Priority review of an NDA with a new molecular entity reduces this time to 6 months following the 60 day filing date (so the goal is a total of 8 months from receipt).

[d]The PDUFA V and VI commitment letters allow FDA to extend the goal date by 3 months if the applicant submits a major amendment to the NDA. FDA may only authorize one extension per review cycle, and extensions should be limited to occasions in which the amendment could lead to approval in the current review cycle.

The fourth key feature of NDAs is whether they qualify for one of FDA's expedited programs. Whether designated as priority or standard, FDA may determine that NDAs for drugs intended to treat serious or life-threatening conditions qualify for development and review under one or

more expedited programs. These programs confer specific benefits with the potential to help reduce the development or review time needed to bring a drug to market. For example, some expedited programs provide for more intensive drug development guidance from FDA officials or allow the applicant to submit completed sections of the NDA for review before submitting the entire application. FDA's expedited programs include accelerated approval, breakthrough therapy designation, and fast track designation.[12] (See table 2.)

Table 2: Expedited Programs for Drug Development and Review by FDA's Center for Drug Evaluation and Research, as of March 2019

Review program	Description
Accelerated approval	Allows drugs for serious or life-threatening diseases or conditions that provide a meaningful advantage over available therapies to be approved based on either a surrogate endpoint or an intermediate clinical endpoint.[a] FDA generally requires that post-approval confirmatory studies be conducted to confirm the anticipated clinical benefit.
Breakthrough therapy designation[b]	Expedites the development and review of drugs that are intended to treat a serious condition, and that have preliminary clinical evidence indicating that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapy.
Fast track designation[b]	Facilitates the development, and expedites the review, of drugs intended to treat serious conditions that demonstrate the potential to address unmet medical needs.

Source: GAO review of Food and Drug Administration (FDA) information. | GAO-20-244

Note: FDA's expedited programs also include priority review designation, which differs from the programs included in this table because it has a time frame for review under FDA's goals in commitment letters associated with the Prescription Drug User Fee Act reauthorizations for fiscal years 2013 through 2017 and fiscal years 2018 through 2022. We do not discuss the limited population pathway for antibacterial and antifungal drugs or the regenerative medicine advance therapy designation because they were beyond the scope of this report.

[a]For accelerated approval, a surrogate endpoint is a marker, such as a laboratory measure or physical sign, that is reasonably likely to predict clinical benefit, but is not itself a measure of clinical benefit. For example, tumor shrinkage in certain cancer types has been considered reasonably likely to predict an improvement in, and can therefore be considered a surrogate endpoint for, overall

[12]Like NDAs, BLAs may qualify for any one or more of these three expedited programs. We refer to accelerated approval, breakthrough therapy designation, and fast track designation as expedited programs to distinguish them from priority review designation, because unlike priority review, these additional expedited programs are not directly related to PDUFA goals. Most priority NDAs qualify for one or more of these three additional expedited programs; conversely, few standard NDAs qualify for any of these three expedited programs. For drugs to qualify for two of these three expedited programs—breakthrough therapy designation and fast track designation—the drug sponsor must request the designation. Although not a focus of our work, we collected data about requests for these expedited program designations and the outcomes of those requests; this information is presented in appendix III. The Cures Act established two additional programs that were beyond the scope of this report—limited population pathway for antibacterial and antifungal drugs, and regenerative medicine advance therapy designation.

survival. Similarly, for this expedited program, an intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity or mortality and is considered reasonably likely to predict the drug's effect on irreversible morbidity or mortality or other clinical benefit. A clinical endpoint is a direct measure of how a patient feels, functions, or survives.

[b]FDA can rescind breakthrough therapy designation or fast track designation if a drug no longer meets the qualifying criteria.

NDAs must include substantial evidence of a drug's effectiveness, which is typically drawn from clinical trials.[13] In traditional clinical trials, patients receiving a new drug are often compared with patients receiving a placebo or a different drug. To maximize data quality, these clinical trials are usually randomized (patients are randomly assigned to either the group receiving the new drug or a comparison group) and double-blinded (neither the patients nor the investigators know who is receiving a particular treatment). According to FDA, although this type of study design is often the most powerful tool for evaluating the safety and effectiveness of new drugs, many traditional clinical trials are becoming more costly and complex to administer. Additionally, according to FDA, many new drugs are not easily evaluated using traditional approaches. For example, drugs intended for patients with rare diseases are difficult to evaluate due to the limited number of patients affected by the disease and available for study.

The Cures Act was enacted on December 13, 2016, to accelerate the discovery, development and delivery of new treatments—including drugs—for patients. Among other things, the Cures Act includes provisions for FDA to evaluate and facilitate the use of evidence from sources other than traditional clinical trials to support safety and effectiveness determinations for new drugs. For example, FDA was directed to evaluate the potential use of evidence based on data that is routinely collected outside of traditional clinical trials from sources such as electronic health records, medical claims data, and disease registries; evidence from such data sources is referred to as real-world evidence. In the commitment letter associated with PDUFA VI, which was enacted on August 18, 2017, the agency agreed to certain goals relating to the use of real-world evidence in regulatory decision-making and also agreed to certain activities intended to facilitate the development and application of

[13]Substantial evidence is defined as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." 21 U.S.C. § 355(d).

an additional source of evidence known as model-informed drug development. Although these nontraditional sources of evidence were included in NDAs prior to the enactment of the Cures Act and PDUFA VI, at the time this legislation was enacted, most of them were not widely used. For example, according to FDA officials, the NDAs that included real-world evidence were generally for drugs to treat oncology diseases or rare diseases.

FDA Divisions Differ in Proportions of NDAs Reviewed with One or More Key Features

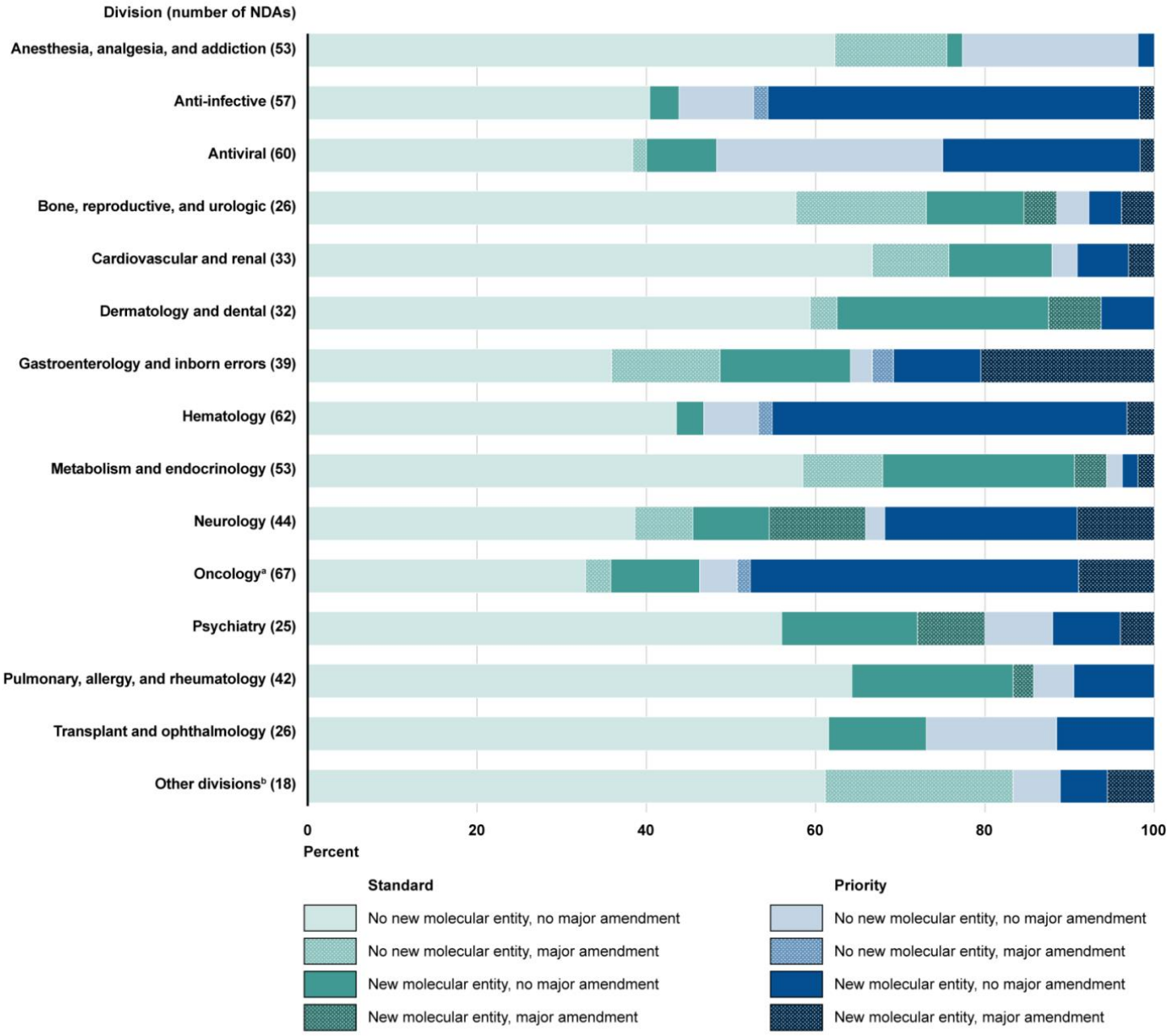
Our analysis of the 637 original NDAs submitted from fiscal years 2014 through 2018 indicates that divisions differed in the proportions of NDAs they reviewed that had any one of three key features that are linked to time frames for initial review under FDA's PDUFA goals. As examples:

- 6 percent of the NDAs reviewed by the dermatology and dental division had a priority review designation, while 56 percent of the NDAs reviewed by the anti-infective division had a priority review designation;
- 4 percent of the NDAs reviewed by the anesthesia, analgesia, and addiction division involved a new molecular entity, while 52 percent of the NDAs reviewed by the neurology division involved one; and
- None of the NDAs reviewed by the transplant and ophthalmology division involved a major amendment, while 36 percent of the applications reviewed by the gastroenterology and inborn errors division involved one.[14]

(See fig. 1. App. IV provides more detailed information about differences between divisions in the number and proportion of NDAs with these key features.)

[14]Of 637 applications, 32 percent had a priority review designation, 36 percent involved a new molecular entity, and 12 percent involved a major amendment.

Figure 1: Proportion of FDA Divisions' New Drug Applications (NDA) with Key Features Linked to Time Frames for Initial Review under FDA's Prescription Drug User Fee Act (PDUFA) V and VI Goals, Fiscal Years 2014 through 2018



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-244

Note: Data are from 637 NDAs that FDA's Center for Drug Evaluation and Research (CDER) received from fiscal years 2014 through 2018 and for which FDA completed its initial review by March 31, 2019. We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER. FDA's time frames for initial review reflect the time frames specified in FDA's goals in commitment letters associated with the PDUFA reauthorizations for fiscal years 2013 through 2017 and fiscal years 2018 through 2022. Key features linked to time frames for initial review are whether the NDA's review designation is priority or standard, whether the NDA involves a new molecular entity or not, and whether the applicant submitted a major amendment or not. An NDA receives a priority review designation if the product would provide significant therapeutic improvements in the safety and effectiveness of the prevention, diagnosis, or treatment of a serious condition when compared to available drugs. Otherwise, it receives a standard review designation. FDA's goal for initial review of a priority NDA is at least 4 months less than for a standard NDA. A new molecular entity is generally an active ingredient that has not been previously approved by FDA or previously marketed as a drug in the United States. FDA's goal for initial review of an NDA with a new molecular entity is 2 months more from the date it receives the application than for NDAs without any new molecular entities. A major amendment to a pending NDA (one under FDA review) is a submission of additional information that may include a major new clinical safety or efficacy study report or major new analyses of studies, among other things. FDA may extend its goal for initial review of an NDA by 3 months if the applicant submits a major amendment while the NDA is under FDA review. FDA's goal for initial review of a standard NDA that does not involve either a new molecular entity or a major amendment is 10 months.

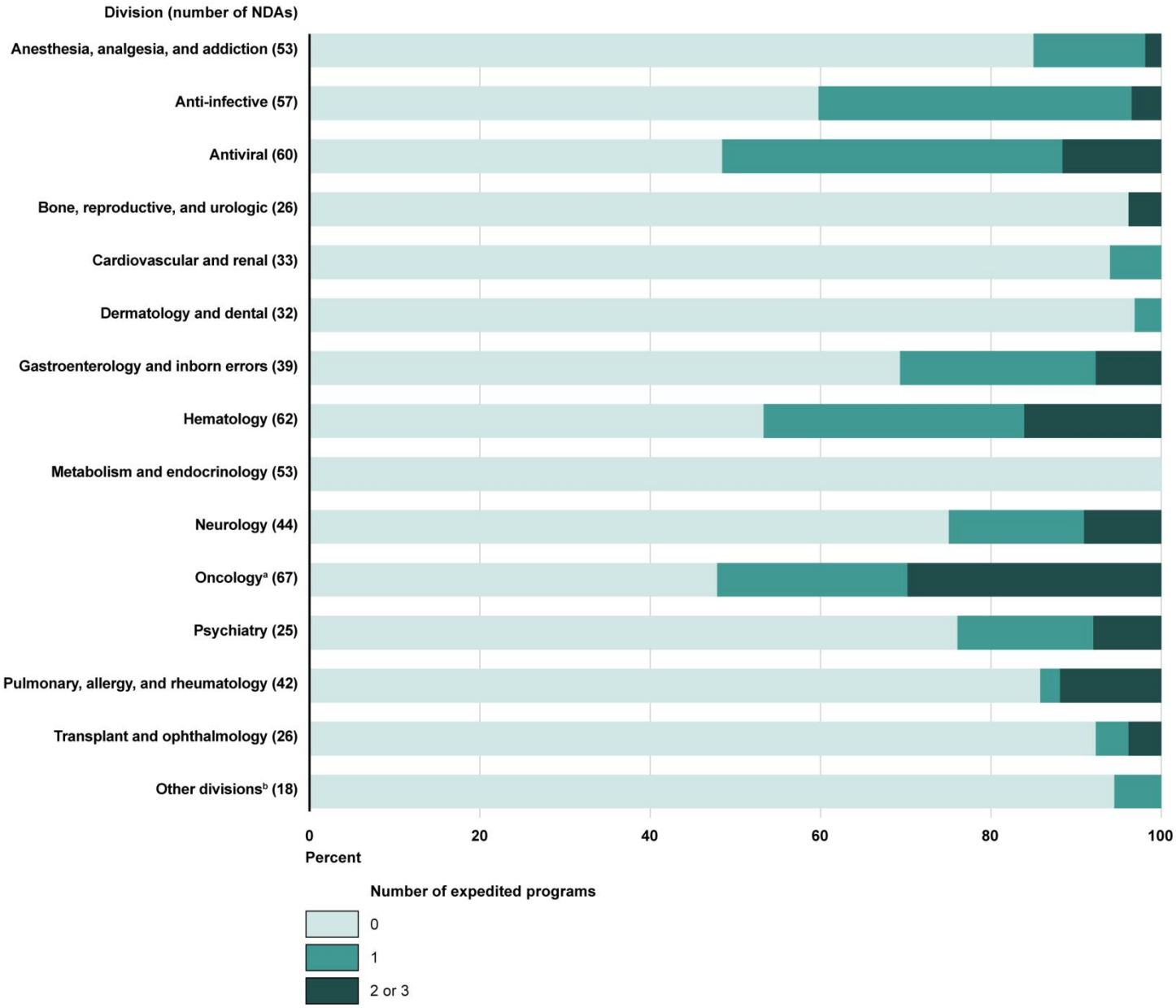
[a]CDER had two oncology divisions; FDA combined the NDAs for those two divisions in the data the agency provided.

[b]Two divisions—the medical imaging and nonprescription drug divisions—each reviewed nine NDAs. We combined them into a single "other divisions" category for our analyses.

We also found differences between divisions in the proportion of NDAs that they reviewed under an expedited program—the fourth key feature of NDAs. For example, none of the NDAs reviewed by the metabolism and endocrinology division qualified for one or more expedited programs, while 52 percent of the NDAs reviewed by the antiviral division qualified for one or more expedited programs.[15] (See fig. 2. App. V provides more detailed information about differences between divisions in the number and proportion of NDAs that qualified for one or more expedited programs.)

[15]Of 637 applications, 18 percent qualified for one expedited program and 9 percent qualified for two or three expedited programs.

Figure 2: Proportion of FDA Divisions' New Drug Applications (NDA) That Qualified for One or More Expedited Programs, Fiscal Years 2014 through 2018



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-244

Note: Data are from 637 NDAs that FDA's Center for Drug Evaluation and Research (CDER) received from fiscal years 2014 through 2018 and for which FDA completed its initial review by March 31, 2019. We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by

CDER. These data represent the proportions of NDAs reviewed by each division that qualified for one or more of three expedited programs: (1) accelerated approval, (2) breakthrough therapy designation, and (3) fast track designation. The accelerated approval program allows drugs for serious or life-threatening diseases or conditions that provide a meaningful advantage over available therapies to be approved based on either a surrogate endpoint or an intermediate clinical endpoint rather than a clinical endpoint (i.e., a direct measure of how a patient feels, functions, or survives). Breakthrough therapy designation expedites the development and review of drugs that are intended to treat a serious condition, and that have preliminary clinical evidence indicating that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapy. Fast track designation facilitates the development, and expedites the review, of drugs intended to treat serious conditions that demonstrate the potential to address unmet medical needs. These programs are intended to help reduce the development or review time needed to bring a drug to market. FDA's expedited programs also include priority review designation, which we analyzed separately because it has a time frame for review under FDA's goals in commitment letters associated with the Prescription Drug User Fee Act reauthorizations for fiscal years 2013 through 2017 and fiscal years 2018 through 2022.

[a]CDER had two oncology divisions; FDA combined the NDAs for those two divisions in the data the agency provided.

[b]Two divisions—the medical imaging and nonprescription drug divisions—each reviewed nine NDAs. We combined them into a single "other divisions" category for our analyses.

It is not unexpected that divisions differ in the proportion of their applications with key features linked to FDA's time frames for review or qualification for expedited programs because the divisions are responsible for different products. For example, some divisions, such as the oncology divisions, regulate products for conditions that are more likely to be serious or life-threatening, and therefore the NDAs reviewed by these divisions are more likely to qualify for priority review designation and expedited programs, compared with other divisions, such as the dermatology and dental division.

FDA Divisions Vary in Their Initial Review Times for NDAs, Largely Due to PDUFA Goals

Our analysis of review times for the 637 original NDAs submitted from fiscal years 2014 through 2018 shows that FDA divisions differed in the number of days they took to complete their initial reviews.[16] For example, the median time taken to complete an initial review of an NDA by the anti-infective division was about 2 months faster than the median time taken by the gastroenterology and inborn errors division. (For more information about initial review times, see app. VI.)

We found, however, that these differences in initial review times largely reflected key features of the NDAs reviewed by the divisions, particularly

[16]FDA completed its initial review of 97 percent of NDAs within the time frames established under its PDUFA goals—a greater percentage than the 90 percent goal stated in its PDUFA V and VI commitment letters.

those features linked to FDA's time frames for review under its PDUFA goals. We analyzed initial review times using a statistical regression with two variables reflecting key features of the NDAs—target time frame for review of the application under FDA's PDUFA goals (in days, from FDA's receipt of the NDA to FDA's targeted date for completion of the initial review) and number of expedited programs (0, 1, or 2 or more)—along with division as independent variables.[17] We found that each of these variables was a significant determinant of initial review times. Specifically, our regression analysis shows that on average

- The shorter the target time frame for initial review of the NDA under FDA's PDUFA goals, the shorter the initial review, and this target time frame was responsible for the majority of variation in initial review times.[18]
- The greater the number of expedited programs for which the NDA qualified, the shorter the time FDA took to complete the initial review.[19]

Controlling for the effects of these key NDA features, however, we found that most of the divisions' average review times were similar to (within 2 weeks of) each other. In contrast, the hematology and oncology divisions reviewed applications a bit more rapidly—about 2 or 3 weeks faster—than

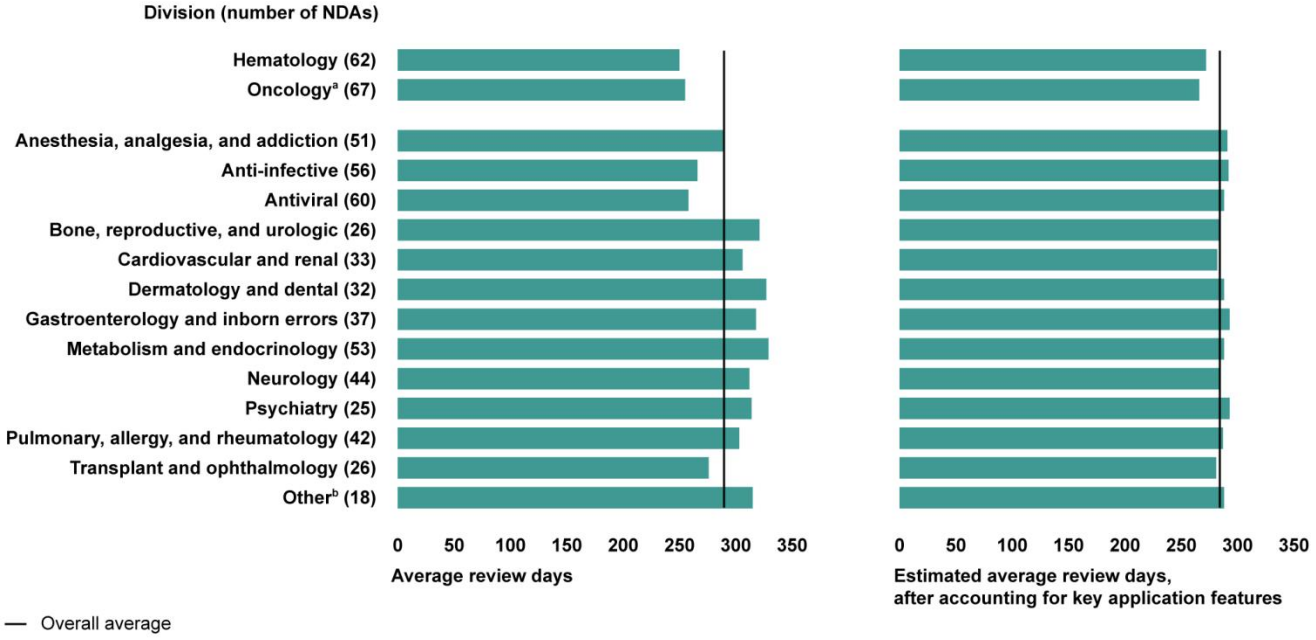
[17]For this regression analysis, we excluded five applications for which unusual conditions resulted in exceptionally long review times in comparison to their targeted dates for review completion.

[18]The three independent variables in our regression analysis—the target time frame for review under FDA's PDUFA goals, number of expedited programs, and division—together accounted for 85 percent of the variance in initial review times. To assess the relative importance of these variables as determinants of initial review times, we conducted additional regressions that included only one independent variable at a time. When we included only the target time frame for review under FDA's PDUFA goals in the regression, it accounted for 82 percent of the variance in initial review times. When we conducted similar regressions for each of the other two variables, they each accounted for less than 25 percent of the variance. We thus concluded that the target time frame for review under FDA's PDUFA goals accounted for the majority of the variance in initial review times.

[19]All else being equal, the expected mean value of a review of an NDA that qualified for one expedited program was 7 days shorter than for reviews of NDAs that did not qualify for an expedited program and the expected mean value of a review of an NDA that qualified for two or three expedited programs was 17 days shorter than reviews of NDAs that did not qualify for an expedited program.

other divisions.[20] Figure 3 illustrates the results of our analyses. The panel on the left shows the variation in the divisions' actual average review times. The panel on the right shows the estimated average review times, after accounting for key application features, that is, what the review times would have been if each division had reviewed equal numbers of applications with these key features.

Figure 3: Actual and Estimated Initial New Drug Application (NDA) Review Times for FDA Divisions, Fiscal Years 2014 through 2018



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-244

Note: Data are from 632 NDAs that FDA's Center for Drug Evaluation and Research (CDER) received from fiscal years 2014 through 2018 and for which FDA completed its initial review by March 31, 2019. We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER. The data do not include five NDAs for which FDA's review times were exceptionally long in comparison to FDA's target time frame for review and for which FDA officials identified unusual circumstances that resulted in substantial delays. We defined the actual initial review time as the number of days from FDA's receipt of the NDA to the agency's completion of the initial review by taking regulatory action. Estimated average review days are based on a regression analysis that

[20]To better understand the effect of division on initial review times, we compared the expected mean value for each division to the overall expected mean value for initial review times. With the exception of hematology and oncology, the expected mean values for initial review times (all else being equal) were from 7 days less to 5 days more than the overall mean, and none of these differences were statistically significant. In contrast, the expected mean value for oncology was 22 days less, and the expected mean value for hematology was 16 days less, than the overall mean. These two expected mean values were statistically different from the overall mean.

included division and two variables reflecting key NDA features: (1) the target time frame for review, counted as the number of days from receipt of the NDA to a target review date reflecting FDA's goals associated with the Prescription Drug User Fee Act reauthorizations for fiscal years 2013 through 2017 and fiscal years 2018 through 2022 and (2) the number of expedited programs for drugs intended to treat serious or life-threatening conditions for which the NDA qualified, counted as 0, 1, or 2 to 3. The estimated average review days from the regression can be understood as showing what the review times would have been if each division had received applications that were comparable in these key features.

[a]CDER had two oncology divisions; FDA combined the NDAs for those two divisions in the data the agency provided.

[b]Two divisions—the medical imaging and nonprescription drug divisions—each reviewed nine NDAs. We combined them into a single "other divisions" category for our analyses.

We asked FDA officials what might contribute to somewhat faster review times by the hematology and oncology divisions, and FDA officials told us that a number of variables could have contributed to these differences. For example, the officials told us that applicants differ in their level of experience, which can affect the quality of the NDA or the speed of response to FDA's requests for information; applications differ in complexity; and the oncology and hematology divisions could differ from others in their risk/benefit considerations. As previously noted, some divisions, such as the oncology divisions, regulate products for conditions that are more likely to be serious or life-threatening compared with other divisions, such as the dermatology and dental division, and risk/benefit considerations can differ across conditions that vary in how serious or life-threatening they are. For example, the potential benefits of drugs that carry substantial risks for dangerous side effects would likely be weighed differently if the drug is intended to address a life-threatening illness for which there is no other treatment than if the drug is intended to address an illness that is not life-threatening or for which there is an alternative treatment.

FDA Is Implementing Initiatives to Evaluate and Facilitate the Use of Different Evidence Sources to Support NDAs

FDA has several initiatives underway to evaluate and facilitate FDA review divisions' and drug sponsors' use of evidence derived from sources other than traditional clinical trials to support NDAs. (See table 3 for a description of these different evidence sources and each initiative.)

Table 3: FDA Initiatives to Evaluate and Facilitate the Use of Different Evidence Sources to Support New Drug Applications

Name of the initiative	Description of the evidence source	Goal of the initiative
Real-World Evidence Program	Real world evidence is clinical evidence about the usage and potential benefits or risks of a drug derived from analyses of real-world data. In contrast to data collected from a traditional clinical trial, real-world data are routinely collected from sources such as electronic health records, medical claims and billing data, and product and disease registries.	To evaluate the potential to use real-world evidence to, among other things, help support regulatory decisions about drug effectiveness, particularly to support labeling changes for approved drugs (e.g., adding or modifying an indication).
Patient-Focused Drug Development	Patient-focused drug development utilizes data—referred to as patient experience data—that are collected by any persons (including patients, caregivers, and others) about patients' experiences with a disease or condition, including their symptoms, the impact of the disease on their functioning and quality of life, and their preferences for treatment. Patient experience data can, among other things, inform the development of clinical outcome assessments that are used to evaluate clinical benefit in clinical trials.	To facilitate the incorporation of the patient's voice in drug development and evaluation, including by facilitating and advancing the use of systematic approaches for collecting and utilizing robust and meaningful patient and caregiver input, including patient experience data, during drug development.
Complex Innovative Trial Designs	Complex innovative trial designs are those with complex or innovative features that have rarely or never been used to date. Complex adaptive designs are an example of this type of trial. Unlike traditional clinical trial designs, in which characteristics of the trial's design—such as the sample size or treatment—are fixed at the start of the trial, an adaptive design adjusts to information that was not available when the trial began.[a]	To facilitate the use of a number of different types of complex innovative trial designs to support regulatory decisions about new drugs and to integrate these approaches across more therapeutic areas.
Drug Development Tool Qualification Programs	Drug development tools are methods, materials, or measures—such as clinical outcome assessments and biomarkers—that facilitate drug development and regulatory review.	To verify that certain drug development tools, including particular biomarkers and clinical outcome assessments, can be relied on to have specific interpretations and applications in drug development and regulatory review, that is, they can be used for specific and identified purposes without further evaluation.[b] Once qualified by FDA, a drug development tool can be used in any drug development program for the qualified context of use without requiring that FDA reconsider and reconfirm its suitability.[c]
Model-Informed Drug Development	Model-informed drug development refers to the use of a wide range of quantitative models, including simulations, in drug development (but excluding statistical designs that require computer simulations to determine the operating characteristics of a confirmatory clinical trial). These models can be used to integrate information from diverse data sources or develop information that cannot, or would not, be generated through clinical trials due to limitations such as a small patient population.	To facilitate the use of model-informed drug development approaches and integrate these approaches into more NDAs across more therapeutic areas.

Source: GAO analysis of Food and Drug Administration (FDA) documents. | GAO-20-244

[a]For example, a trial might begin with a particular outcome of interest and patients assigned to one of three dose formulations of a particular drug but, based on an interim analysis of data from the trial, the outcome may be modified and doses not demonstrating promising results may be dropped.

[b]A biomarker is a biological characteristic, such as blood pressure, that can be measured to indicate normal biological processes, pathogenic processes, or responses to an exposure or intervention and includes a surrogate endpoint. A clinical outcome assessment is a measure of how a patient feels, functions, or survives. FDA's qualification initiative also includes a qualification program for animal models, which are used for testing medical countermeasures.

[c]Context of use refers to a comprehensive description that fully and clearly delineates the limits of FDA's qualification decision in terms of the manner and purpose of use for the drug development tool. The qualified context of use defines the boundaries within which the available data adequately justify use of the drug development tool.

According to FDA officials, implementing these initiatives can help ensure that when drug sponsors utilize these sources of evidence in NDAs, the evidence is of sufficient quality to be used in regulatory decision-making and that there is consistency across FDA review divisions in their evaluation of the evidence. FDA officials also said that although complex innovative trial designs might replace traditional clinical trials as evidence in NDAs, real-world evidence is more likely to be used to supplement clinical trial data.

Although the initiatives are not restricted to any particular type of disease or patient population, according to FDA officials, some initiatives may be more relevant for certain types of diseases or patient populations than others. For example, according to FDA officials:

- real-world evidence may be most relevant for diseases that have outcomes that are consistently collected in the health care system.
- clinical outcome assessments (one aspect of patient-focused drug development) may be most relevant for diseases that are chronic, symptomatic, or affect functioning and activities of daily living.
- complex innovative trial designs may be most relevant for situations in which the population size is small or limited, such as pediatric populations, or where there is an unmet medical need, such as rare diseases.

Our review of FDA documentation and interviews with FDA officials show that FDA has taken steps to implement each of these five initiatives. These steps include conducting public workshops with key stakeholders, issuing guidance for industry and FDA staff, initiating pilot programs, and developing FDA staff capacity, including by providing training and other educational resources. (See table 4 for examples of key activities by initiative.) These and future planned activities—including issuing additional guidance and revising relevant FDA policies and procedures—are intended to address deliverables for FDA to accomplish through 2021

that are outlined in the Cures Act and the PDUFA VI commitment letter. According to FDA officials, the agency intends to meet these deliverables, though, according to these officials, some of the activities implemented under the initiatives, such as certain pilot programs, will likely extend beyond 2021.

Table 4: Examples of Key Activities Implemented under FDA Initiatives to Evaluate and Facilitate the Use of Different Evidence Sources to Support Drug Applications, as of December 2019

Name of the initiative	Examples of key activities to date
Real-World Evidence Program	FDA issued a framework for the agency's real-world evidence program. The framework includes information on sources of real-world evidence; gaps in data-collection activities; standards and methods for collecting and analyzing real-world evidence; and current pilot programs.
Patient-Focused Drug Development	FDA issued two of four guidance documents that will describe, in a stepwise manner, how stakeholders can collect and submit patient experience data and other relevant information from patients and caregivers for drug development and regulatory decision-making.
Complex Innovative Trial Designs	FDA launched a pilot program to provide an opportunity for drug sponsors—entities seeking to market their drugs—and FDA staff to discuss the application of complex innovative trial design approaches in the context of specific drug development programs. Drug sponsors in the pilot program participate in two meetings with FDA staff that occur within approximately 120 days of each other. Additionally, to encourage use of complex innovative trial designs across therapeutic areas, FDA may present certain agreed-upon aspects of a drug sponsor's trial as a case study for shared learning.
Drug Development Tool Qualification Programs	To promote transparency and shared learning with drug sponsors, FDA started providing information on the agency's website about each submission under the qualification process, as well as a comprehensive list of all drug development tools qualified under the program and all surrogate endpoints that were the basis of approval or licensure of a drug.[a]
Model-Informed Drug Development	FDA launched a pilot program to provide an opportunity for drug sponsors and FDA staff to discuss the application of model-informed drug development approaches in the context of specific drug development programs. Drug sponsors in the pilot program participate in two meetings with FDA staff that occur within approximately 120 days of each other.

Source: GAO analysis of Food and Drug Administration (FDA) documents. | GAO-20-244

[a]A surrogate endpoint is a marker, such as a laboratory measure or physical sign, that is reasonably likely to predict clinical benefit, but is not itself a measure of clinical benefit. For example, tumor shrinkage in certain cancer types has been considered reasonably likely to predict an improvement in, and can therefore be considered a surrogate endpoint for, overall survival.

Although implementation is still in progress for all of the initiatives, FDA officials reported some outcomes. For example, since the launch of the model-informed drug development pilot program, the agency has received two NDA supplements that incorporated model-informed drug development concepts discussed during pilot program meetings.[21] Additionally, officials told us there has been a recent increase in investigational new drug submissions utilizing complex innovative trial

[21]An NDA supplement is submitted to propose changes to an approved drug's labeling, such as adding or modifying an indication or claim, revising the dose or dose regimen, providing for a new route of administration, or changing the marketing status from prescription to over-the-counter use.

designs. FDA officials also reported an increase in biomarker submissions under the drug development tool qualification program, and continued growth of the clinical outcome assessment qualification program. FDA expects that fully implementing the initiatives will lead to further increases in the use of evidence from sources other than traditional clinical trials.

Agency Comments

We provided a draft of this report to the Department of Health and Human Services for review and comment. The department provided technical comments, which we incorporated as appropriate.

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

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or 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 VII.

John E. Dicken
Director, Health Care

Appendix I: Methodology for Data Analyses

To determine (1) how Food and Drug Administration (FDA) divisions differ in the proportion of new drug applications (NDA) they review with key features linked to review time goals and expedited programs and (2) how FDA review divisions differ in the time taken to complete initial reviews and the extent to which key features of NDAs contribute to those differences, we analyzed data from FDA. We also interviewed FDA officials about the data and their review processes.

Data

We obtained data regarding all NDAs submitted to FDA's Center for Drug Evaluation and Research (CDER) from fiscal years 2014 through 2018.[1] These data included information about features that distinguish NDAs from one another, including which division was responsible for the review. The data also included information through March 31, 2019, about the dates when FDA received and completed a review of each NDA, along with the target dates for completion of review under FDA's goals in commitment letters associated with the Prescription Drug User Fee Act (PDUFA) reauthorizations for fiscal years 2013 through 2017 (PDUFA V) and fiscal years 2018 through 2022 (PDUFA VI).[2]

To ensure meaningful analysis of review times, we excluded NDAs for which FDA had not completed an initial cycle of review. Of 686 NDAs submitted in fiscal years 2014 through 2018, the applicant withdrew 10 NDAs prior to completion of FDA's initial review and 39 NDAs were still

[1]Fiscal year 2018 was the most recent year for which complete data were available at the time of our review. We included biologic license applications (BLA) reviewed by CDER, and excluded BLAs reviewed by FDA's Center for Biologics Evaluation and Research. We refer to all CDER's NDAs and BLAs as NDAs.

[2]See FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, accessed Nov. 5, 2019, https://www.fda.gov/media/81306/download; FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022, accessed Nov. 5, 2019, https://www.fda.gov/media/99140/download.

under FDA review as of March 31, 2019, leaving 637 NDAs for which FDA had completed an initial review.[3]

To assess the reliability of these data, we conducted a series of electronic and logic tests to identify missing data or other anomalies. These analyses were informed by our review of relevant documentation and interviews with knowledgeable FDA officials. As part of our assessment of reliability, we worked with FDA to identify and correct information about certain NDAs in a small number of instances in which we identified discrepancies. Using these methods, we determined that the remaining data were sufficiently reliable for our purposes. Unless otherwise specified, the results we present are statistically significant at the 0.05 level.

Proportions of NDAs with Key Features

To determine how FDA divisions differ in the proportion of NDAs they review with key features linked to FDA's time frames for initial reviews and expedited programs, we conducted a series of chi-square tests comparing the distributions of the 637 NDAs with and without specific features across divisions. These key features included:

- whether the NDA had a priority review designation (a designation applied by FDA if the product would provide a significant therapeutic improvement in the safety and effectiveness of the prevention, diagnosis, or treatment of a serious condition when compared to available drugs) or instead had a standard designation;
- whether the NDA did or did not involve a new molecular entity—an active ingredient that had not previously been marketed or approved for use as a drug in the United States,
- whether the NDA did or did not involve a major amendment (a submission, while a pending NDA is under FDA review, of additional

[3]One NDA that had been withdrawn by the applicant after FDA began its review was then later resubmitted. We did not include this NDA in our analyses. Upon receipt of an NDA, FDA begins a 60 calendar day filing review. During this filing review, the agency determines whether the application is sufficiently complete to permit a substantive review. If not, or if the applicant has not paid the full user fee (or is in arrears for prior unpaid user fees), the agency refuses to file the application. Applicants may also withdraw their applications prior to the end of the filing review. We excluded NDAs that were received, but not filed. Of the 686 applications submitted to CDER in fiscal years 2014 through 2018, 63 were BLAs.

information that may include a major new clinical safety or efficacy study report or major new analyses of studies, among other things); and

- whether the NDA did or did not qualify for an expedited program (accelerated approval, breakthrough therapy designation, or fast track designation), programs intended to help reduce the time involved in developing or reviewing certain drugs that have the potential to treat serious or life-threatening conditions.[4]

(See table 5 for relevant statistics from these chi-square tests.)

Table 5: Results of Tests Comparing FDA Divisions in Their Distributions of New Drug Applications (NDA) with and without Specific Key Features

Feature	Chi-square	P-value[a]
Priority review designation[b]	102.81	0.0001
New molecular entity[c]	66.39	0.0001
Major amendment[d]	55.66	0.0001
Expedited program[e]	119.40	0.0001

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-244

Note: Data are from 637 NDAs that FDA's Center for Drug Evaluation and Research (CDER) received from fiscal years 2014 through 2018 and for which FDA completed its initial review by March 31, 2019. We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER.

[a]Results were significant at or below the listed p-value.

[b]NDAs differ in whether they do or do not receive a priority review designation, which they generally receive if the product would provide significant therapeutic improvements in the safety and effectiveness of the prevention, diagnosis, or treatment of a serious condition when compared to available drugs. Otherwise, it receives a standard review designation.

[c]NDAs differ in whether they do or do not include a new molecular entity—an active ingredient that has not been previously approved by FDA or previously marketed as a drug in the United States.

[4]The data indicated whether or not FDA extended its target time frame for review of the NDA by 3 months, as allowed under its PDUFA goals if the applicant submitted a major amendment while the NDA was pending (i.e., while under FDA review). Thus, our data reflect only those major amendments that were accepted by FDA and resulted in a 3-month extension to the target time frame for review. A small number of NDAs receive priority review designation because the applicant uses a priority review voucher. FDA awards priority review vouchers to drug sponsors that develop and receive approval for certain products for tropical diseases, rare pediatric diseases, and medical countermeasures. A priority review voucher entitles the voucher holder to receive a 6-month priority review, rather than the typical 10-month standard review, for a future drug application for a drug to treat any disease or condition. Seven priority review vouchers were redeemed for NDAs reviewed by FDA's CDER in fiscal years 2014 through 2018. Under FDA's PDUFA goals, BLAs are treated like NDAs involving a new molecular entity and, like those NDAs, may receive a priority review designation and may be the subject of a major amendment. Similarly, like NDAs, BLAs may qualify for one or more expedited programs.

[d]NDAs differ in whether they do or do not involve a major amendment—a submission of additional information that may include a major new clinical safety or efficacy study report or major new analyses of studies, among other things—while the NDA is under FDA review.

[e]NDAs differ in whether FDA determined that they qualified for no expedited program or qualified for one or more of three expedited programs: (1) accelerated approval; (2) breakthrough therapy designation; and (3) fast track designation. The accelerated approval program allows drugs for serious or life-threatening diseases or conditions that provide a meaningful advantage over available therapies to be approved based on either a surrogate endpoint or an intermediate clinical endpoint rather than a clinical endpoint (i.e., a direct measure of how a patient feels, functions, or survives). Breakthrough therapy designation expedites the development and review of drugs that are intended to treat a serious condition, and that have preliminary clinical evidence indicating that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapy. Fast track designation facilitates the development, and expedites the review, of drugs intended to treat serious conditions that demonstrate the potential to address unmet medical needs. FDA's expedited programs also include priority review designation, which we analyzed separately because it has a time frame for review under FDA's goals in commitment letters associated with the Prescription Drug User Fee Act reauthorizations for fiscal years 2013 through 2017 and fiscal years 2018 through 2022.

Initial Review Times

To determine how FDA review divisions differ in the time taken to complete initial reviews, we conducted a preliminary regression analysis of 637 NDAs with the number of days an FDA division took to complete its initial review as the dependent variable and division as a single independent variable. We defined the time to complete a review as the number of days from FDA's receipt of the NDA to the agency's completion of the initial review by taking regulatory action.

To determine the extent to which key NDA features contributed to differences between divisions in the time taken to complete initial reviews, we conducted a multiple regression analysis of the number of days FDA took to complete its initial review with division as an independent variable, along with two other independent variables to control for the key NDA features:

- **Target time frame for initial review of the NDA under FDA's PDUFA goals.** Three key NDA features are linked to time frames for FDA's initial review under its PDUFA goals—whether the NDA was priority or standard, did or did not involve a new molecular entity, and did or did not involve a major amendment. To control for these three features simultaneously, we counted the number of days from FDA's receipt of the NDA until FDA's target date for completion of the initial review under FDA's PDUFA goals, and used that variable—the target time frame for review under FDA's PDUFA goals—as an independent

variable.[5] We identified five NDAs for which FDA's review time was exceptionally long in comparison to the target time frame for review under its PDUFA goals, and we asked FDA officials about them. FDA officials stated that these reviews were substantially delayed because of complicated manufacturing site issues, complicated legal and regulatory issues, or emerging public health issues requiring last minute advisory committee meetings—conditions that we deemed sufficiently unusual to exclude these five NDAs from further statistical analyses of review times.[6]

- **Number of expedited programs for which the NDA qualified.** Another key NDA feature is whether it qualified for one or more expedited programs, programs with the potential to help reduce the development or review time needed to bring a drug to market. We controlled for this feature by including number of expedited programs (0, 1, or 2 or more) as an independent variable in our multiple regression analysis.

Thus, we tested the effect of division on initial review times for 632 NDAs while controlling for the target time frame for review under FDA's PDUFA goals and qualification for expedited programs.[7] (See tables 6 and 7 for relevant statistics from this multiple regression analysis.)

[5]We counted the days from receipt to the target date under FDA's PDUFA goals. For NDAs that do not involve a new molecular entity, the PDUFA goal specifies the time frame for review starting with the date of receipt. For NDAs that involve new molecular entities and BLAs, the PDUFA goal specifies the time frame for review starting with the filing date, which is 60 days after the date of receipt, and so the time frame for review of NDAs that involve new molecular entities and BLAs under FDA's PDUFA goals can also be counted from the date of receipt by including the 60-day filing review period.

[6]We also asked FDA officials about five NDAs that were reviewed well in advance of the target time frame for review under FDA's PDUFA goals. The reasons FDA officials provided for these review times included familiarity with previously approved products and the absence of a currently approved treatment for a serious and life-threatening condition. We did not exclude these NDAs from our analyses because they did not indicate unusual or exceptional conditions.

[7]If FDA does not approve an NDA at the end of a review cycle, the applicant may choose to revise the NDA (for example, by adding information to address identified deficiencies) and resubmit it for another cycle of review. Of the 637 NDAs for which FDA had completed its initial review, there were 99 NDAs for which a second cycle of review had been completed by March 31, 2019. We subjected these second cycle review times to an analysis parallel to our analysis of initial review times, and again found that the effect of target time frames for that cycle's review under FDA's PDUFA goals was significant, $F = 312.92$, $p < 0.0001$, and was largely responsible for differences in those review times.

Table 6: Tests of the Effect of Variables Linked to FDA's Target Time Frames for Review, Expedited Programs, and Division on Initial FDA Review Times

Independent variable	F-test	P-value[a]
Number of days to the target date for completion of the review[b]	2,222.65	0.0001
Number of expedited programs[c]	9.06	0.0001
Division[d]	4.22	0.0001

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-244

Note: Data were from 632 new drug applications (NDA) that FDA's Center for Drug Evaluation and Research (CDER) received from fiscal years 2014 through 2018 and for which FDA completed its initial review by March 31, 2019. We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER. Results are from a multiple regression analysis of the times it took FDA to complete initial reviews of NDAs with three independent variables—the number of days to the target date for completion of the review, number of expedited programs, and division.

[a]Results were significant at or below the listed p-value.

[b]The target date for completion of the review reflects the time frames specified in FDA's goals in commitment letters associated with the Prescription Drug User Fee Act reauthorizations for fiscal years 2013 through 2017 and fiscal years 2018 through 2022; FDA's goal is to complete 90 percent of reviews of applicable NDAs within the specified time frames. For initial reviews, this time frame reflects three key features of the NDA: (a) whether the NDA received a priority review designation, which is provided if the product would provide significant therapeutic improvements in the safety and effectiveness of the prevention, diagnosis, or treatment of a serious condition when compared to available drugs; (b) whether the drug covered by the NDA included a new molecular entity—an active ingredient that has not been previously approved by FDA or previously marketed as a drug in the United States; and (c) whether the NDA involved a major amendment—a submission of additional information that may include a major new clinical safety or efficacy study report or major new analyses of studies, among other things, while the NDA is pending, that is, while under FDA review.

[c]NDAs differ in whether they qualified for no expedited program or qualified for one or more of three expedited programs: (1) accelerated approval; (2) breakthrough therapy designation; and (3) fast track designation. The accelerated approval program allows drugs for serious or life-threatening diseases or conditions that provide a meaningful advantage over available therapies to be approved based on either a surrogate endpoint or an intermediate clinical endpoint rather than a clinical endpoint (i.e., a direct measure of how a patient feels, functions, or survives). Breakthrough therapy designation expedites the development and review of drugs that are intended to treat a serious condition, and that have preliminary clinical evidence indicating that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapy. Fast track designation facilitates the development, and expedites the review, of drugs intended to treat serious conditions that demonstrate the potential to address unmet medical needs. For this multiple regression analysis, we distinguished among NDAs that did not qualify for any of these programs, NDAs that qualified for one and only one of these programs, and NDAs that qualified for two or three of these programs. FDA's expedited programs also include priority review designation, which we analyzed separately because it has a time frame for review under FDA's goals in commitment letters associated with the Prescription Drug User Fee Act reauthorizations for fiscal years 2013 through 2017 and fiscal years 2018 through 2022.

[d]During the time period for which we obtained data, CDER had 17 reviewing divisions, but our analysis included 15: FDA combined the NDAs for its two oncology divisions in the data the agency provided, and two divisions—the medical imaging and nonprescription drug divisions—each reviewed nine NDAs, so we combined them into a single "other divisions" category for our analyses.

Table 7: Results of Comparisons of Each Division's Initial Review Times to the Overall Average Initial Review Time

Division	t-test	P-value[a]
Anesthesia, analgesia, and addiction	0.44	n.s.
Anti-infective	0.51	n.s.
Antiviral	-0.04	n.s.
Bone, reproductive, and urologic	-0.36	n.s.
Cardiovascular and renal	-0.74	n.s.
Dermatology and dental	-0.04	n.s.
Gastroenterology and inborn errors	0.65	n.s.
Hematology	-2.21	0.05
Metabolism and endocrinology	-0.02	n.s.
Neurology	-0.47	n.s.
Oncology[b]	-3.08	0.01
Psychiatry	0.60	n.s.
Pulmonary, allergy, and rheumatology	-0.12	n.s.
Transplant and ophthalmology	-0.82	n.s.

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-244

Note: Data were from 632 new drug applications (NDA) that FDA's Center for Drug Evaluation and Research (CDER) received from fiscal years 2014 through 2018 and for which FDA completed its initial review by March 31, 2019. We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER. Results are from a multiple regression analysis of the times it took FDA to complete initial reviews of NDAs with three independent variables: number of days to the target date for completion of the review under FDA's goals in commitment letters associated with the Prescription Drug User Fee Act reauthorizations for fiscal years 2013 through 2017 and fiscal years 2018 through 2022, number of expedited programs, and division. Two divisions—the medical imaging and nonprescription drug divisions—each reviewed nine NDAs; we combined them into a single "other" category for this analysis that served as the statistical comparison point for our comparisons and so is not included in the table.

[a]We present results that are statistically significant at the 0.05 level and use "n.s." to indicate non-significant results. Results were significant at or below the listed p-value.

[b]CDER had two oncology divisions; FDA combined data from NDAs for its two oncology divisions in the data the agency provided.

Our multiple regression analysis allowed us to test a specific hypothesis about the effect of division on review times, namely, whether divisions differed in their review times after controlling for the key features of NDAs. This regression analysis did not test a model of review times—that is, we did not attempt to identify all variables that affect review times, nor did we seek to identify the specific set or combination of variables within our data that had maximum explanatory power. Our analyses indicated that variation remained in initial review times, even after we controlled for these variables. It is important to note that an array of factors might be expected to influence review times, including not just those factors that

were captured in our analysis, but also factors such as state of the science and quality of the application.

With data from 632 NDAs distributed unevenly across 15 divisions, meaningful tests of additional variables or their interactions were not possible.[8] Nonetheless, we conducted exploratory analyses that included other potentially relevant variables in addition to the target time frame for review under FDA's PDUFA goals, number of expedited programs, and division. In separate regression analyses, we examined (a) the fiscal year in which FDA received the NDA and (b) whether the application was a BLA, an NDA based on information from studies conducted by the applicant, or an NDA based on at least some information from studies not conducted by or for the applicant.[9] We did not find evidence of a consistent effect of either of these additional factors on review times, but in light of the number of NDAs, we cannot exclude the possibility that one or more of these factors affects review times. In a third exploratory analysis, we examined the outcome of the initial review—(a) approval; (b) tentative approval, which FDA grants if the NDA meets requirements for approval, but cannot be approved due to a patent or exclusivity period for a listed drug; or (c) issuance of a letter to the applicant called a complete response letter, in which FDA describes the specific deficiencies the agency identified and recommends ways to make the application viable for approval. This analysis suggested that NDAs that were approved for marketing at the end of the initial cycle of review were reviewed slightly faster on average than other NDAs, but this result should be viewed with caution because a small number of NDAs with certain initial review outcomes were distributed unequally. For example, very few of the NDAs (11) reviewed through one or more expedited programs resulted in tentative approval.

[8]During the time period for which we obtained data, CDER had 17 review divisions, including two oncology divisions; FDA combined the NDAs for those two divisions in the data they provided, leaving 16 review divisions. Two of the remaining divisions—the medical imaging and nonprescription drug divisions—each reviewed only nine NDAs. We combined them into a single "other divisions" category for our regression analyses.

[9]Under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, NDAs may rely, at least in part, on investigations that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted..." See 21 U.S.C. § 355(b)(2). For example, such an application may rely on the finding of safety or effectiveness for an approved product or on published literature in addition to studies conducted by the sponsor.

Appendix II: Total Times Taken by FDA Divisions to Review New Drug Applications Received in Fiscal Years 2014 through 2018

The Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) divisions differed in the total number of days they took to complete reviews of 637 new drug applications (NDA) submitted from fiscal years 2014 through 2018 and completed by March 31, 2019.[1] (See fig. 4.) Importantly, these times reflect differences associated with the number of completed review cycles, FDA's target time frames for review under its goals in commitment letters associated with the Prescription Drug User Fee Act (PDUFA) reauthorizations for fiscal years 2013 through 2017 (PDUFA V) and fiscal years 2018 through 2022 (PDUFA VI), and number of expedited programs.[2]

- **Number of review cycles.** The number of cycles of review to which the NDAs we examined were subject was largely dependent on factors that were not under FDA's control, namely, the applicant's actions and timing. When a cycle of review ends with an FDA action, that action can be (a) approval, which allows the applicant to market the drug, (b) tentative approval, which FDA grants if the NDA meets requirements for approval, but cannot be approved due to a patent or exclusivity period for a listed drug, or (c) issuance of a letter to the

[1]We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER.

[2]See FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, accessed Nov. 5, 2019, https://www.fda.gov/media/81306/download; FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022, accessed Nov. 5, 2019, https://www.fda.gov/media/99140/download.

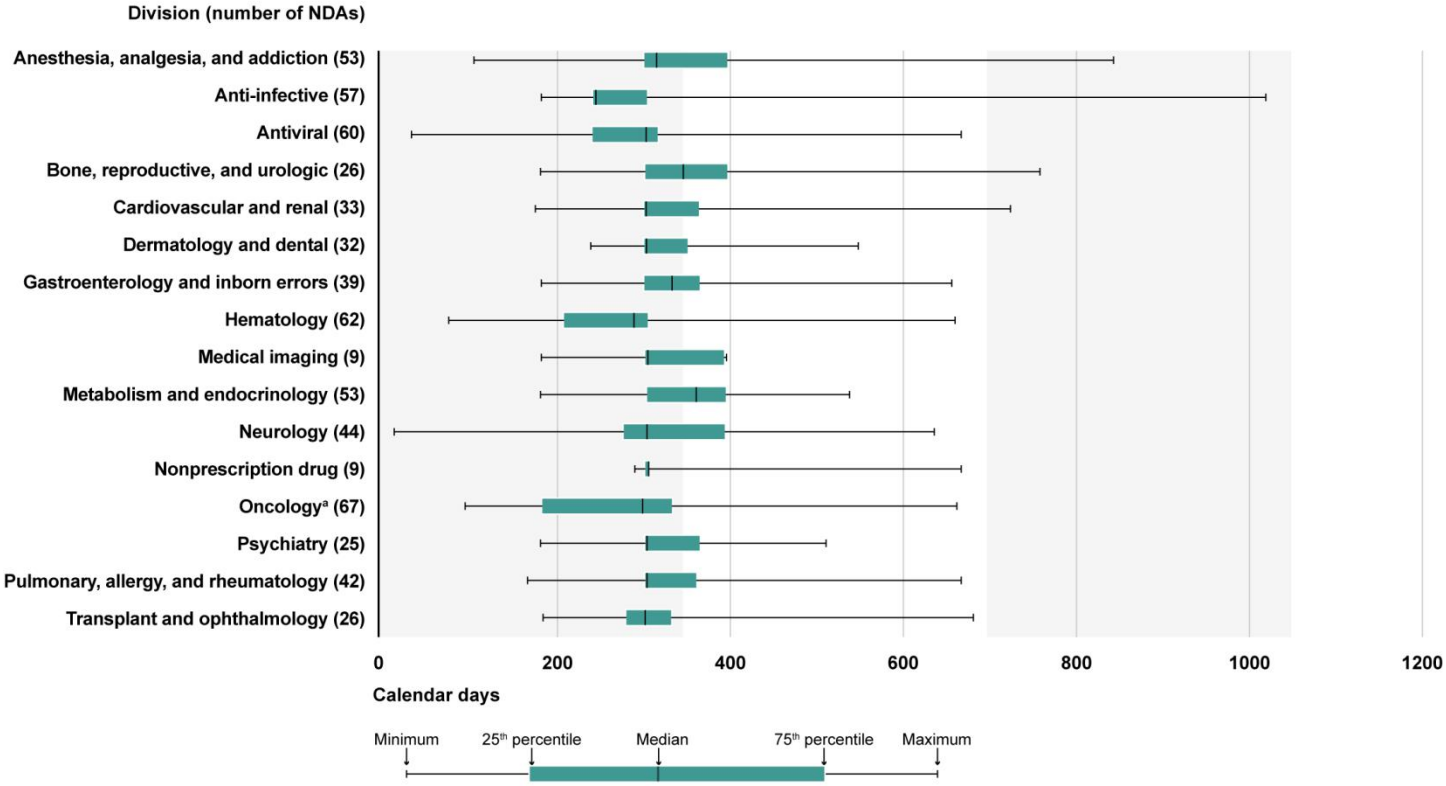
applicant called a complete response letter, in which FDA describes the specific deficiencies the agency identified and recommends ways to make the application viable for approval. The applicant may respond to either tentative approval or a complete response letter by resubmitting a revised application, triggering a new cycle of review; it is up to the applicant to decide whether to resubmit the application.[3] In addition, NDAs that were submitted earlier in time would have a greater chance of being resubmitted and reviewed by March 31, 2019, than applications submitted later in time. The number of completed review cycles ranged from one to four cycles:

  - 637 NDAs went through a completed first (initial) cycle review;
  - 99 of those 637 NDAs went through a completed second cycle review;
  - 20 of those 99 NDAs went through a completed third cycle review; and
  - 3 of those 20 NDAs went through a completed fourth cycle review.

- **Target time frames for review.** Review times reflect differences in time frames for review under FDA's PDUFA goals. The target time frames for review ranged from less than 6 months to 15 months for the first cycle and from less than 2 months to 9 months for later cycles of review.
- **Number of expedited programs.** These review times also reflect differences associated with the number of FDA's expedited programs for which NDAs qualified. In general, these expedited programs are designed to help reduce the development or review time needed for drugs intended to treat serious or life-threatening conditions.

[3]If the applicant does not resubmit the application within one year, the agency construes the absence of a reply as a request for withdrawal.

Figure 4: Total Days for Completed Review Cycles by FDA Divisions for New Drug Applications (NDA) Originally Submitted from Fiscal Years 2014 through 2018



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-244

Note: Data are from 637 NDAs that FDA's Center for Drug Evaluation and Research (CDER) received from fiscal years 2014 through 2018 and for which FDA completed its initial review by March 31, 2019. We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER. Review times reflect time actually under FDA review during from one to four separate, completed cycles of review (the initial review and review of up to three resubmissions) and have not been adjusted to reflect differences between divisions in key features of the applications they received.

[a]CDER had two oncology divisions; FDA combined the NDAs for those two divisions in the data the agency provided.

Appendix III: Requests for Breakthrough Therapy and Fast Track Designations, Fiscal Years 2013 through 2018

Two of the Food and Drug Administration's (FDA) expedited programs for new drugs intended to treat serious or life-threatening conditions—breakthrough therapy designation and fast track designation—must be requested by the drug sponsor. These programs are intended to help reduce the development or review time needed to bring a drug to market by offering benefits such as more intensive drug development guidance from FDA officials or by allowing the applicant to submit completed sections of the NDA for review before submitting the entire application. The request is normally made while the drug sponsor is conducting clinical trials or when seeking FDA's permission to collect clinical trial data, although the request may also be made when submitting a new drug application (NDA) or while the NDA is under review.[1]

FDA's Center for Drug Evaluation and Research (CDER) divisions are responsible for determining whether requests qualify for these expedited programs based on evidence the drug sponsors provide in support of the requests. To qualify for breakthrough therapy designation, the drug sponsor must present preliminary clinical evidence involving one or more clinically significant endpoints that indicate that the drug may demonstrate substantial improvement over available therapies. To qualify for fast track designation, the drug sponsor must either provide evidence demonstrating the drug's potential to address unmet need or document that the drug is designated as a qualified infectious disease product. FDA may grant or deny the request, or the drug sponsor may withdraw the

[1]To obtain the full benefits of breakthrough therapy designation, drug sponsors should normally request that designation before they initiate one or more of the clinical trials intended to serve as the primary basis for demonstration of efficacy. To obtain the full benefits of fast track designation, drug sponsors should normally request that designation before submitting an NDA.

request before FDA renders a decision. If FDA grants the designation, the drug sponsor may subsequently withdraw from the designation, or FDA may rescind either designation if the drug no longer meets the qualifying criteria.

We obtained data regarding all requests for breakthrough therapy and fast track designations submitted to CDER from fiscal years 2013 through 2018.[2] These data included information about which division was responsible for the review and the outcome of the request—whether it was granted or denied or whether the drug sponsor withdrew the request before FDA reached a decision. To assess the reliability of these data, we conducted a series of electronic and logic tests to identify missing data or other anomalies. These analyses were informed by our review of relevant documentation and interviews with knowledgeable FDA officials. Using these methods, we determined that the data were sufficiently reliable for our purposes. We examined these data to determine whether there were any material differences between divisions in the frequency of possible outcomes. Our analyses focused on the outcomes and did not allow us to determine whether divisions differed in their application of the stated criteria.

Breakthrough therapy designation. We found few differences across divisions in the frequency of the possible outcomes of requests for breakthrough therapy designation:

- Of 634 requests for breakthrough therapy designation (including nine requests submitted with or after the NDA submission), 39 percent were granted, 48 percent were denied, and 13 percent were withdrawn by the drug sponsor before FDA reached a decision.
- Divisions differed widely in the number of requests for breakthrough therapy designation they received, from 0 for the nonprescription drug division to 102 for one of FDA's two oncology divisions.
- With two exceptions, the numbers of these requests that were granted, denied, or withdrawn for each division were similar to what would be expected based on the overall frequency of the possible outcomes. Requests to the hematology division were withdrawn more frequently than requests to other divisions (32 percent) and that division denied requests less frequently (17 percent) than other divisions. The neurology division denied more (81 percent), and

[2]Fiscal year 2018 was the most recent year for which complete data were available at the time of our review.

granted fewer (13 percent), requests for breakthrough therapy designation than other divisions.

- Within the time period we studied, the drug sponsor withdrew from breakthrough therapy designation after it was granted in six cases and FDA rescinded the designation in 14 cases.

Fast track designation. Similarly, we found few differences across divisions in the frequency of the possible outcomes of requests for fast track designation:

- Of 965 requests for fast track designation (including 35 requests submitted with or after the NDA submission), 71 percent were granted, 24 percent were denied, and 5 percent were withdrawn by the drug sponsor before FDA reached a decision.
- Again, divisions differed widely in the number of requests for fast track designation they received, from 2 for the nonprescription drug division to 133 for the neurology division.
- The numbers of these requests that were granted, denied, or withdrawn for each division were generally similar to what would be expected based on the overall frequency of the possible outcomes, although the anti-infective division granted more (91 percent), and denied fewer (6 percent), requests for fast track designation than other divisions.
- Within the time period we studied, no drug sponsor withdrew from fast track designation after it was granted, nor did FDA rescind any such designation.

Appendix IV: New Drug Applications with Key Features Linked to Time Frames for Review, Fiscal Years 2014 through 2018

Pursuant to the Prescription Drug User Fee Act (PDUFA) and its subsequent reauthorizations, the Food and Drug Administration (FDA) collects user fees from drug sponsors to supplement its annual appropriation for salaries and expenses.[1] As part of each reauthorization process, FDA identifies goals in a commitment letter to Congress, including goals for the time the agency takes to complete reviews of different types of drug applications upon initial submission and resubmission.[2] In general, these goals identify a percentage of certain types applications that FDA is expected to review within specified target time frames. For initial NDA reviews—reviews of the NDA as originally submitted—FDA's target time frames for review that would meet its PDUFA goals vary and are linked to three key NDA features that reflect the drug or the applicant's action: (1) whether or not the application receives priority review designation, which indicates that the drug could provide significant therapeutic improvements in the safety and

[1]See Federal Food, Drug, and Cosmetic Act Amendments, Pub. L. No. 102-571, tit. I, 106 Stat. 4491, 4491-4500 (1992); Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, tit. I, subtit. A, 111 Stat. 2296, 2298-2305 (1997); Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, tit. V, subtit. A, 116 Stat. 594, 687-694 (2002); Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, tit. I, 121 Stat. 823, 825-842 (2007); Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, tit. I, 126 Stat. 993, 996-1002 (2012); FDA Reauthorization Act of 2017, Pub. L. No. 115-52, tit. I, 131 Stat. 1005, 1006-1013 (2017).

[2]See, for example, FDA, *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017*, accessed Nov. 5, 2019, https://www.fda.gov/media/81306/download; FDA, *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022*, accessed Nov. 5, 2019, https://www.fda.gov/media/99140/download.

effectiveness of the prevention, diagnosis, or treatment of a serious condition when compared to available drugs; (2) whether or not the application involves a new molecular entity—an active ingredient that has not been previously marketed or approved for use in the United States; and (3) whether or not the applicant submitted a major amendment while the NDA was pending, that is, while under FDA's review.[3] The target time frame for review for any specific NDA reflects all three of these features. Reviews are conducted by one of the agency's Center for Drug Evaluation and Research (CDER) divisions, each of which specialize in a specific group of drug products, such as hematology or neurology.

As shown in table 8, divisions differed in the numbers and proportions of NDAs they reviewed that had the features linked to time frames for review under FDA's PDUFA goals.

Table 8: Number and Proportion of FDA Division's New Drug Applications (NDA) with Key Features Linked to Time Frames for Initial Review under FDA's Prescription Drug User Fee Act (PDUFA) V and VI Goals, Fiscal Years 2014 through 2018

Number of NDAs (percentage of the division's NDAs)[a]

	Standard				Priority				Total
	No new molecular entity		New molecular entity		No new molecular entity		New molecular entity		
Division	**No MA**	**MA**	**No MA**	**MA**	**No MA**	**MA**	**No MA**	**MA**	
Anesthesia, analgesia, and addiction	33 (62)	7 (13)	1 (2)	0 (0)	11 (21)	0 (0)	1 (2)	0 (0)	**53 (100)**
Anti-infective	23 (40)	0 (0)	2 (4)	0 (0)	5 (9)	1 (2)	25 (44)	1 (2)	**57 (100)**
Antiviral	23 (38)	1 (2)	5 (8)	0 (0)	16 (27)	0 (0)	14 (23)	1 (2)	**60 (100)**
Bone, reproductive and urologic	15 (58)	4 (15)	3 (12)	1 (4)	1 (4)	0 (0)	1 (4)	1 (4)	**26 (100)**
Cardiovascular and renal	22 (67)	3 (9)	4 (12)	0 (0)	1 (3)	0 (0)	2 (6)	1 (3)	**33 (100)**
Dermatology and dental	19 (59)	1 (3)	8 (25)	2 (6)	0 (0)	0 (0)	2 (6)	0 (0)	**32 (100)**
Gastroenterology and inborn errors	14 (36)	5 (13)	6 (15)	0 (0)	1 (3)	1 (3)	4 (10)	8 (21)	**39 (100)**
Hematology	27 (44)	0 (0)	2 (3)	0 (0)	4 (6)	1 (2)	26 (42)	2 (3)	**62 (100)**

[3]Because the goal for NDAs that involve new molecular entities also covers biologic license applications (BLA), we included them with NDAs that involve a new molecular entity. We use the term NDA to include BLAs reviewed by CDER.

	Standard				Priority				Total
	No new molecular entity		New molecular entity		No new molecular entity		New molecular entity		
Division	**No MA**	**MA**	**No MA**	**MA**	**No MA**	**MA**	**No MA**	**MA**	
Metabolism and endocrinology	31 (58)	5 (9)	12 (23)	2 (4)	1 (2)	0 (0)	1 (2)	1 (2)	**53 (100)**
Neurology	17 (39)	3 (7)	4 (9)	5 (11)	1 (2)	0 (0)	10 (23)	4 (9)	**44 (100)**
Oncology[b]	22 (33)	2 (3)	7 (10)	0 (0)	3 (4)	1 (1)	26 (39)	6 (9)	**67 (100)**
Psychiatry	14 (56)	0 (0)	4 (16)	2 (8)	2 (8)	0 (0)	2 (8)	1 (4)	**25 (100)**
Pulmonary, allergy, and rheumatology	27 (64)	0 (0)	8 (19)	1 (2)	2 (5)	0 (0)	4 (10)	0 (0)	**42 (100)**
Transplant and ophthalmology	16 (62)	0 (0)	3 (12)	0 (0)	4 (15)	0 (0)	3 (12)	0 (0)	**26 (100)**
Other divisions[c]	11 (61)	4 (22)	0 (0)	0 (0)	1 (6)	0 (0)	1 (6)	1 (6)	**18 (100)**
Total	**314 (49)**	**35 (5)**	**69 (11)**	**13 (2)**	**53 (8)**	**4 (1)**	**122 (19)**	**27 (4)**	**637 (100)**

Legend: MA = major amendment

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-244

Note: Data are from 637 NDAs that FDA's Center for Drug Evaluation and Research (CDER) received from fiscal years 2014 through 2018 and for which FDA completed its initial review by March 31, 2019. We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER. FDA's time frames for initial review reflect the time frames specified in FDA's goals in commitment letters associated with the PDUFA reauthorizations for fiscal years 2013 through 2017 and fiscal years 2018 through 2022. Key features linked to time frames for initial review under FDA's PDUFA goals are whether the NDA's review designation is priority or standard, whether the NDA involves a new molecular entity or not, and whether the applicant submitted a major amendment or not. An NDA generally receives a priority review designation if the product would provide significant therapeutic improvements in the safety and effectiveness of the prevention, diagnosis, or treatment of a serious condition when compared to available drugs. Otherwise, it receives a standard review designation. FDA's goal for initial review of a priority NDA is at least 4 months less than for a standard NDA. A new molecular entity is generally an active ingredient that has not been previously approved by FDA or previously marketed as a drug in the United States. FDA's goal for initial review of an NDA with a new molecular entity is 2 months more from the date it receives the application than for NDAs without any new molecular entities. A major amendment to a pending NDA (one under FDA review) is a submission of additional information that may include a major new clinical safety or efficacy study report or major new analyses of studies, among other things. FDA may extend its goal for initial review of an NDA by 3 months if the applicant submits a major amendment while the NDA is under FDA review. FDA's goal for initial review of a standard NDA that does not involve either a new molecular entity or a major amendment is 10 months.

[a]Percentages may not add to 100 because of rounding.

[b]CDER had two oncology divisions; FDA combined the NDAs for those two divisions in the data the agency provided.

[c]Two divisions—the medical imaging and nonprescription drug divisions—each reviewed nine NDAs. We combined them into a single "other divisions" category for our analyses.

Appendix V: New Drug Applications That Qualified for Expedited Programs, Fiscal Years 2014 through 2018

The Food and Drug Administration (FDA) may determine that NDAs for drugs intended to treat serious or life-threatening conditions qualify for one or more expedited programs. These programs confer specific benefits with the potential to help reduce the development or review time needed to bring a drug to market, for example, some expedited programs provide for more intensive drug development guidance from FDA officials or allow the applicant to submit completed sections of the NDA for review before submitting the entire application. FDA's expedited programs include accelerated approval, breakthrough therapy designation, and fast track designation.[1] Reviews are conducted by one of the agency's Center for Drug Evaluation and Research (CDER) divisions, each of which specialize in a specific group of drug products, such as hematology or neurology.

As shown in table 9, divisions differed in the proportions of NDAs they reviewed that qualified for expedited programs.[2]

[1]FDA's expedited programs also include priority review designation, which differs from the programs included in this appendix because it is associated with a time frame for review under FDA's goals in commitment letters associated with the Prescription Drug User Fee Act reauthorizations for fiscal years 2013 through 2017 and fiscal years 2018 through 2022. We do not discuss two other programs—the limited population pathway for antibacterial and antifungal drugs or the regenerative medicine advance therapy designation—because they were beyond the scope of this report.

[2]We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER.

Table 9: Number and Proportion of FDA Division's New Drug Applications (NDA) That Qualified for Expedited Programs, Fiscal Years 2014 through 2018

Number of NDAs (percentage of the division's NDAs)[a]. Number of expedited programs.

Division	0	1	2 or 3	Total
Anesthesia, analgesia, and addiction	45 (85)	7 (13)	1 (2)	**53 (100)**
Anti-infective	34 (60)	21 (37)	2 (4)	**57 (100)**
Antiviral	29 (48)	24 (40)	7 (12)	**60 (100)**
Bone, reproductive and urologic	25 (96)	0 (0)	1 (4)	**26 (100)**
Cardiovascular and renal	31 (94)	2 (6)	0 (0)	**33 (100)**
Dermatology and dental	31 (97)	1 (3)	0 (0)	**32 (100)**
Gastroenterology and inborn errors	27 (69)	9 (23)	3 (8)	**39 (100)**
Hematology	33 (53)	19 (31)	10 (16)	**62 (100)**
Metabolism and endocrinology	53 (100)	0 (0)	0 (0)	**53 (100)**
Neurology	33 (75)	7 (16)	4 (9)	**44 (100)**
Oncology[b]	32 (48)	15 (22)	20 (30)	**67 (100)**
Psychiatry	19 (76)	4 (16)	2 (8)	**25 (100)**
Pulmonary, allergy, and rheumatology	36 (86)	1 (2)	5 (12)	**42 (100)**
Transplant and ophthalmology	24 (92)	1 (4)	1 (4)	**26 (100)**
Other divisions[c]	17 (94)	1 (6)	0 (0)	**18 (100)**
Total	**469 (74)**	**112 (18)**	**56 (9)**	**637 (100)**

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-244

Note: Data are from 637 NDAs that FDA's Center for Drug Evaluation and Research (CDER) received from fiscal years 2014 through 2018 and for which FDA completed its initial review by March 31, 2019. We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER. These data represent the numbers and proportions of NDAs reviewed by each division that qualified for none, or one, or two or three of three expedited programs: (1) accelerated approval; (2) breakthrough therapy designation; and (3) fast track designation. The accelerated approval program allows drugs for serious or life-threatening diseases or conditions that provide a meaningful advantage over available therapies to be approved based on either a surrogate endpoint or an intermediate clinical endpoint rather than a clinical endpoint (i.e., a direct measure of how a patient feels, functions, or survives). Breakthrough therapy designation expedites the development and review of drugs that are intended to treat a serious condition, and that have preliminary clinical evidence indicating that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapy. Fast track designation facilitates the development, and expedites the review, of drugs intended to treat serious conditions that demonstrate the potential to address unmet medical needs. FDA's expedited programs also include priority review designation, which we analyzed separately because it has a time frame for review under FDA's goals in commitment letters associated with the Prescription Drug User Fee Act reauthorizations for fiscal years 2013 through 2017 and fiscal years 2018 through 2022.

[a]Percentages may not add to 100 because of rounding.

[b]CDER had two oncology divisions; FDA combined the NDAs for those two divisions in the data the agency provided.

[c]Two divisions—the medical imaging and nonprescription drug divisions—each reviewed nine NDAs. We combined them into a single "other divisions" category for our analyses.

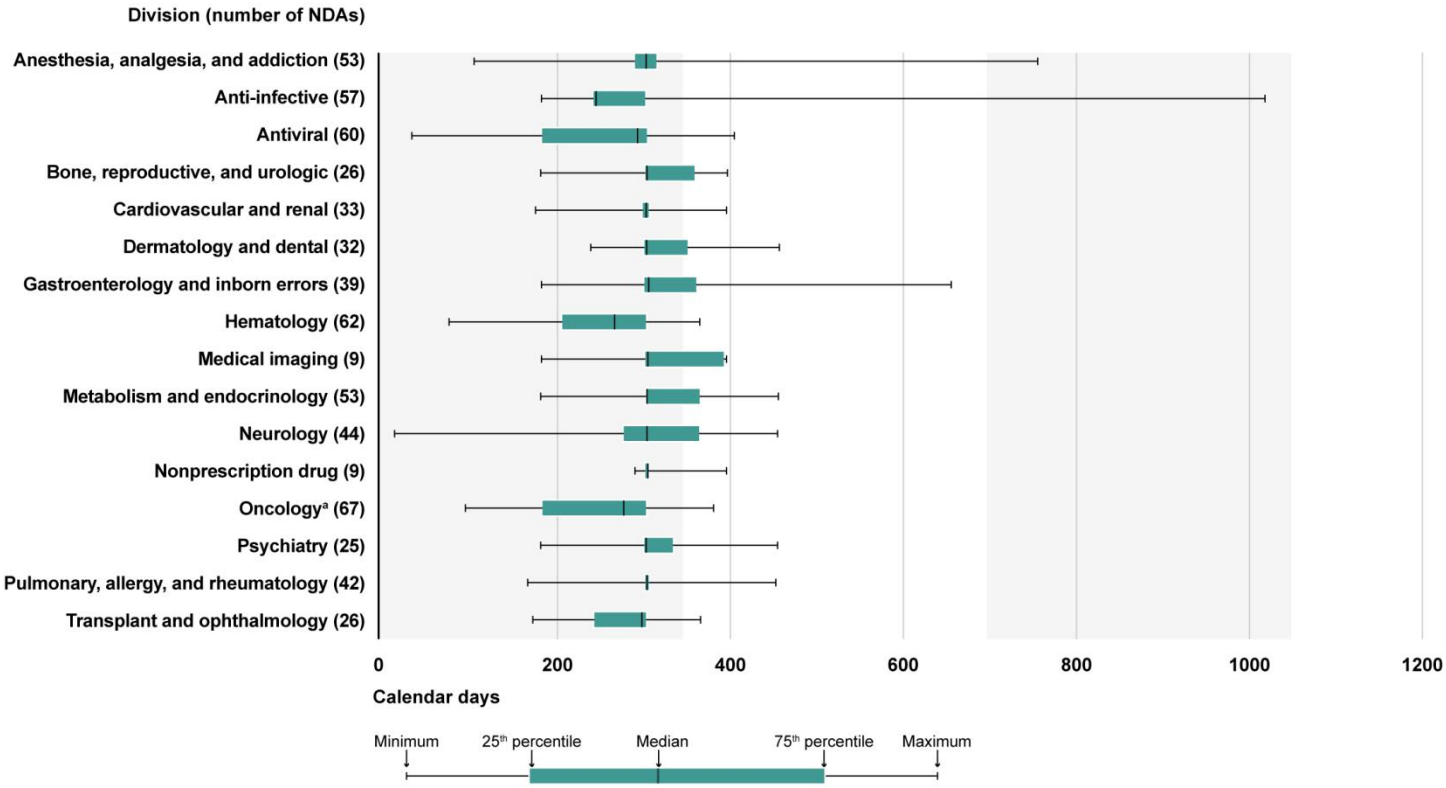
Appendix VI: Times Taken to Complete Initial Reviews of New Drug Applications Received from Fiscal Year 2014 through 2018

The Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) divisions differed in the total number of days they took to complete initial reviews of new drug applications (NDA) received from fiscal years 2014 through 2018 and completed by March 31, 2019.[1] (See fig. 5.) These review times reflect differences associated with FDA's target time frames for initial review under its goals in commitment letters associated with the Prescription Drug User Fee Act (PDUFA) reauthorizations for fiscal years 2013 through 2017 (PDUFA V) and fiscal years 2018 through 2022 (PDUFA VI).[2] These target time frames for review are linked to specific features of the NDA and ranged from less than 6 months to 15 months for the initial review. These review times also reflect differences associated with the number of expedited programs for which NDAs qualified.

[1]We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER.

[2]See FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017, accessed Nov. 5, 2019, https://www.fda.gov/media/81306/download; FDA, PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 Through 2022, accessed Nov. 5, 2019, https://www.fda.gov/media/99140/download.

Figure 5: Total Days for an Initial Review by FDA Divisions for New Drug Applications (NDA) Submitted from Fiscal Years 2014 through 2018



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-20-244

Note: Data are from 637 NDAs that the FDA's Center for Drug Evaluation and Research (CDER) received from fiscal years 2014 through 2018 and for which FDA completed its initial review by March 31, 2019. We use the term NDA to include NDAs and biologic license applications (BLA) reviewed by CDER. Review times have not been adjusted to reflect differences between divisions in key features of the applications they received.

[a]CDER had two oncology divisions; FDA combined the NDAs for those two divisions in the data the agency provided.

Appendix VII: 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, William Hadley (Assistant Director), Geri Redican-Bigott (Assistant Director), Aubrey Naffis (Analyst-in-Charge), and Kristen Joan Anderson made key contributions to this report. Also contributing were Sam Amrhein, Todd D. Anderson, Leia Dickerson, Kaitlin Farquharson, Rich Lipinski, and Ethiene Salgado-Rodriguez.

Appendix VIII: Accessible Data

Data Tables

Data Table for Figure 1: Proportion of FDA Divisions' New Drug Applications (NDA) with Key Features Linked to Time Frames for Initial Review under FDA's Prescription Drug User Fee Act (PDUFA) V and VI Goals, Fiscal Years 2014 through 2018

Division (number of NDAs)	Standard, not NME, no extension	Standard, not NME, extension	Standard, NME, no extension	Standard, NME, extension	Priority, not NME, no extension	Priority not NME, extension	Priority, NME, no extension	Priority NME, extension
Anesthesia, Analgesia, and Addiction (53)	33	7	1	0	11	0	1	0
Anti-infective (57)	23	0	2	0	5	1	25	1
Antiviral (60)	23	1	5	0	16	0	14	1
Bone, Reproductive, and Urologic (26)	15	4	3	1	1	0	1	1
Cardiovascular and Renal (33)	22	3	4	0	1	0	2	1
Dermatology and Dental (32)	19	1	8	2	0	0	2	0
Gastroenterology and Inborn Errors (39)	14	5	6	0	1	1	4	8
Hematology (62)	27	0	2	0	4	1	26	2
Metabolism and Endocrinology (53)	31	5	12	2	1	0	1	1
Neurology (44)	17	3	4	5	1	0	10	4
Oncology (67)	22	2	7	0	3	1	26	6
Psychiatry (25)	14	0	4	2	2	0	2	1
Pulmonary, Allergy, and Rheumatology (42)	27	0	8	1	2	0	4	0
Transplant and Ophthalmology (26)	16	0	3	0	4	0	3	0
Other Divisions (18)	11	4	0	0	1	0	1	1

Data Table for Figure 2: Proportion of FDA Divisions' New Drug Applications (NDA) That Qualified for One or More Expedited Programs, Fiscal Years 2014 through 2018

Division	Number of NDAs	No expedited programs	1 expedited program	2 or 3 expedited programs
Anesthesia, analgesia, and addiction	53	45	7	1
Anti-infective	57	34	21	2
Antiviral	60	29	24	7
Bone, reproductive, and urologic	26	25	0	1
Cardiovascular and renal	33	31	2	0
Dermatology and dental	32	31	1	0
Gastroenterology and inborn errors	39	27	9	3
Hematology	62	33	19	10
Metabolism and endocrinology	53	53	0	0
Neurology	44	33	7	4
Oncology	67	32	15	20
Psychiatry	25	19	4	2
Pulmonary, allergy, and rheumatology	42	36	1	5
Transplant and ophthalmology	26	24	1	1
Other divisions	18	17	1	0

Data Table for Figure 3: Actual and Estimated Initial New Drug Application (NDA) Review Times for FDA Divisions, Fiscal Years 2014 through 2018

Division (number of NDAs)	Actual	Predicted
Hematology (62)	250	272
Oncology[a] (67)	255	266
Anesthesia, analgesia, and addiction (51)	289	291
Anti-infective (56)	266	292
Antiviral (60)	258	288
Bone, reproductive, and urologic (26)	321	285
Cardiovascular and renal (33)	306	282
Dermatology and dental (32)	327	288
Gastroenterology and inborn errors (37)	318	293
Metabolism and endocrinology (53)	329	288
Neurology (44)	312	285
Psychiatry (25)	314	293
Pulmonary, allergy, and rheumatology (42)	303	287
Transplant and ophthalmology (26)	276	281
Other divisions[b] (18)	315	288
Overall average	*289.58*	*284.22*

Data Table for Figure 4: Total Days for Completed Review Cycles by FDA Divisions for New Drug Applications (NDA) Originally Submitted from Fiscal Years 2014 through 2018

Calendar days.

Division	Number of NDAs	Minimum	25th percentile	Median	75th percentile	Maximum
		104	301	315	397	843
Anti-infective	57	182	242	245	304	1,019
Antiviral	60	32	241	303	317	667
Bone, Reproductive, and Urologic	26	181	302	346	397	758
Cardiovascular and Renal	33	175	301	303	364	724
Dermatology and Dental	32	239	301	304	351	548
Gastroenterology and Inborn Errors	39	182	301	333	365	656
Hematology	62	75	208	289	305	660
Medical Imaging	9	182	302	305	393	396
Metabolism and Endocrinology	53	181	304	361	395	538
Neurology	44	12	277	304	394	636
Nonprescription Drug	9	290	302	306	306	667
Oncology[a]	67	94	183	299	333	662
Psychiatry	25	181	302	304	365	511
Pulmonary, Allergy, and Rheumatology	42	166	302	304	361	667
Transplant and Ophthalmology	26	184	280	302	332	681

Data Table for Figure 5: Total Days for an Initial Review by FDA Divisions for New Drug Applications (NDA) Submitted from Fiscal Years 2014 through 2018

Division	Number of NDAs	Minimum	25th percentile	Median	75th percentile	Maximum
		104	290	303	315	756
Anti-infective	57	182	242	245	302	1,019
Antiviral	60	32	183	293	304	405
Bone, Reproductive, and Urologic	26	181	302	304	359	397
Cardiovascular and Renal	33	175	299	303	306	396
Dermatology and Dental	32	239	301	304	351	457
Gastroenterology and Inborn Errors	39	182	301	306	361	656
Hematology	62	75	206	267	303	365
Medical Imaging	9	182	302	305	393	396
Metabolism and Endocrinology	53	181	303	304	365	456
Neurology	44	12	277	304	365	455
Nonprescription Drug	9	290	302	305	306	396
Oncology[a]	67	94	183	277	303	381
Psychiatry	25	181	301	303	334	455
Pulmonary, Allergy, and Rheumatology	42	166	302	304	306	453
Transplant and Ophthalmology	26	172	243	298	303	366

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