United States Government Accountability Office

Report to Congressional Requesters

November 2018

ORPHAN DRUGS

FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue

Accessible Version

GAO-19-83

GAO Highlights

Highlights of GAO-19-83, a report to congressional requesters

November 2018

ORPHAN DRUGS

FDA Could Improve Designation Review Consistency; Rare Disease Drug Development Challenges Continue

Why GAO Did This Study

The ODA provides incentives, including tax credits and exclusive marketing rights, for manufacturers to develop drugs to treat rare diseases, which are typically defined as affecting fewer than 200,000 people in the United States. Approximately 7,000 rare diseases affect an estimated 30 million people in the United States, and only 5 percent of rare diseases have FDA-approved treatments.

GAO was asked to examine FDA's orphan drug processes. In this report, GAO examines, among other things, (1) the actions FDA has taken to address the growing demand for orphan designations; (2) the extent to which FDA has used consistent criteria and complete information in reviewing orphan designation applications; and (3) the steps FDA has taken to address rare disease drug development challenges. GAO analyzed FDA documents and data, as well as all designation review templates FDA completed as of March 2018 for applications received from October to December 2017. GAO interviewed agency officials, as well as stakeholders, including drug manufacturers, industry experts, and patient advocacy groups.

What GAO Recommends

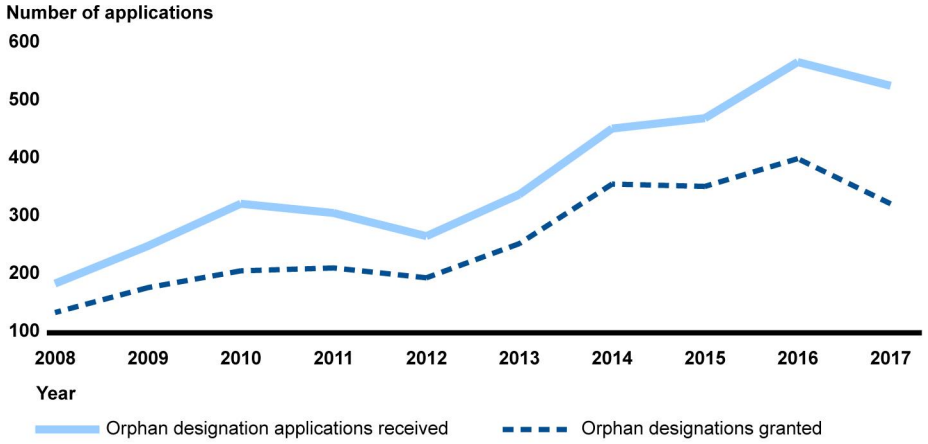
FDA should ensure that all required information for reviews of orphan designation applications is consistently recorded and evaluated. The agency concurred with our recommendation.

View GAO-19-83. For more information, contact John E. Dicken at (202) 512-7114 or dickenj@gao.gov.

What GAO Found

The Food and Drug Administration's (FDA) Office of Orphan Products Development is responsible for reviewing drug manufacturer applications for orphan designation. Drugs granted this designation treat rare diseases and may receive various incentives under the Orphan Drug Act (ODA). As the number of orphan designation applications received and granted has grown, FDA outlined several process changes in its June 2017 modernization plan to improve designation review timeliness and consistency.

Orphan Designation Applications Received and Designations Granted from 2008 to 2017, as of April 2018



Source: GAO analysis of Food and Drug Administration data. | GAO-19-83

In evaluating designation applications, FDA reviewers generally apply two consistent criteria—(1) the size of the rare disease population, and (2) the scientific rationale that the drug may effectively treat the disease. To inform their evaluation, reviewers must record certain background information in a standard review template, such as the drug's U.S. marketing history. Officials told us this information provides important context, such as whether FDA has experience with a little known disease, critical to ensuring a complete designation application review. However, GAO's analysis of 148 designation review templates found that FDA does not consistently record or evaluate background information when making designation decisions. For example, 48 of 148 review templates GAO analyzed were missing information on the drug's U.S. marketing history. As such, FDA cannot be sure that reviewers are conducting complete evaluations that include all critical information needed for assessing its criteria.

Stakeholders GAO interviewed and research GAO reviewed identified a number of rare disease drug development challenges, such as the difficulty in recruiting small populations for clinical trials, with differing opinions about the ODA incentives. For example, several stakeholders were critical of manufacturers obtaining multiple orphan designations—and ODA incentives—for the same drug when the drug may otherwise be profitable from treating multiple patient groups. However, many patient advocacy groups noted that granting ODA incentives in these circumstances is needed to encourage drug manufacturers to study the safety and efficacy of drugs in rare disease populations.

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Abbreviations

BLA	biologic license application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
NDA	new drug application
ODA	Orphan Drug Act
OOPD	Office of Orphan Products Development

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U.S. GOVERNMENT ACCOUNTABILITY OFFICE
441 G St. N.W.
Washington, DC 20548

November 30, 2018

The Honorable Orrin G. Hatch
President Pro Tempore
United States Senate

The Honorable Claire McCaskill
Ranking Member
Committee on Homeland Security and Governmental Affairs
United States Senate

The Honorable Frank Pallone, Jr.
Ranking Member
Committee on Energy and Commerce
House of Representatives

The Honorable Tom Cotton
United States Senate

The Honorable Charles E. Grassley
United States Senate

According to the National Institutes of Health, there are approximately 7,000 rare diseases affecting an estimated 30 million people in the United States. A rare disease or condition (hereafter, "disease") is typically defined as affecting fewer than 200,000 people in the United States, and these diseases are often serious or life-threatening. Currently, only about 5 percent of rare diseases have treatments approved by the Food and Drug Administration (FDA).

The Orphan Drug Act (ODA) was enacted in 1983 to provide drug manufacturers with incentives for developing treatments for small patient populations that were not expected to be profitable.[1] The ODA, as amended, provides incentives for drug manufacturers to develop drugs and biologics (hereafter referred to collectively as "drugs") to treat rare

[1]Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified in pertinent part as amended at 21 U.S.C. §§ 360aa et seq and 26 U.S.C. § 45C).

diseases.[2] These incentives include tax credits and exclusive marketing rights.[3] In order to obtain the incentives, drug manufacturers must submit an application to FDA for orphan designation—a status given to a drug that is intended to treat a rare disease. To receive orphan designation, a drug manufacturer must provide evidence demonstrating that its drug meets certain criteria specified in the ODA and FDA's implementing regulations.

Demand for orphan designations has grown substantially since the ODA's enactment, with the number of designation applications nearly tripling over the past decade. Separate from orphan designation, FDA also determines which drugs may be marketed in the United States, based on evidence of safety and effectiveness.[4] The number of orphan drugs FDA has approved for marketing has also increased over time, with 77 marketing approvals in 2017. According to FDA, the growth in orphan designations and marketing approvals is expected to continue, partly due to medical advances that make health care more personalized, genetically targeted, and likely to address rare diseases.[5] However, the growth in orphan designations and marketing approvals has coincided with questions about FDA's orphan drug program, including that drug development challenges remain for the majority of rare diseases.

[2]Drug manufacturers can also obtain ODA incentives for products used to diagnose or prevent rare disease. For the purposes of this report, we use "treatment" to include diagnosis, prevention, and treatment.

Biologics are derived from living sources (such as humans, animals, and microorganisms), unlike drugs, which are chemically synthesized. Biologics include a wide range of products, such as blood, vaccines, and allergenic products. See 42 U.S.C. § 262(i).

[3]Specifically, for drugs obtaining an orphan designation, drug manufacturers can obtain tax credits for 25 percent of qualified clinical testing expenses for the taxable year, a waiver of certain fees associated with applications for FDA drug marketing approval, and 7 years of exclusive marketing rights (a period of protection from competition). In addition, the Secretary of Health and Human Services may make grants to and enter into contracts with public and private entities to defray the costs of development. See 26 U.S.C. § 45C(a); 21 U.S.C. §§ 379h(a)(1)(F), 360cc(a), and 360ee(a).

[4]Before a new drug can be marketed in the United States, it must be approved by FDA, which evaluates a drug application to determine whether the new drug is safe and effective for its intended use.

[5]EvaluatePharma reports that, by 2024, orphan drugs are expected to capture a fifth of worldwide prescription drug sales ($262 billion). See EvaluatePharma, *Orphan Drug Report 2018* (May 2018).

Due to the importance of rare disease drug development, you requested that we provide information on drugs receiving orphan designations and marketing approvals, and examine certain aspects of FDA's orphan drug processes. In this report, we examine

1. actions FDA has taken to address the growing demand for orphan designations;
2. the extent to which FDA has used consistent criteria and complete information to review applications for orphan designation, and the characteristics of drugs seeking orphan designation;
3. the orphan drugs FDA has approved for marketing; and
4. the steps FDA has taken to address challenges in rare disease drug development.

To examine the actions FDA has taken to address the growing demand for orphan designations, we reviewed agency plans for meeting this demand and reports on timeliness metrics used to track designation reviews. We also reviewed the agency's plans for staffing levels and expertise devoted to reviewing orphan designation applications. In addition, we reviewed its plan for additional programmatic actions to meet designation demand and the mechanisms the agency has in place to respond to orphan drug issues. To describe the rate of demand for orphan designation over time, we obtained and analyzed FDA data over the past 10 years from the agency's internal database on orphan designation applications. Specifically, we determined the number of designation applications received each year from January 1, 2008, to December 31, 2017, and the rate of growth in applications and designations granted during this time frame. We assessed the reliability of data from FDA's internal database on orphan designation applications by interviewing agency officials knowledgeable about the data, reviewing related documentation, and performing electronic data testing for obvious errors, and accuracy and completeness, where applicable. We determined that the data were sufficiently reliable for the purposes of our reporting objectives. We also interviewed FDA officials about how it determines staffing levels given the growing demand for orphan designation reviews. Finally, we interviewed two former Directors of FDA's orphan drug program for their views on the level of resources dedicated over time to FDA's orphan designation process.

To examine the extent to which FDA has used consistent criteria and complete information to evaluate applications for orphan designation, we reviewed designation criteria detailed in the ODA, program regulations,

and agency guidance, as well as documentation of the agency's review process. Specifically, we reviewed guidance for orphan designation reviewers consisting of training and job aids, and a standard form used for evaluating applications. We also assessed the extent to which reviewers consistently documented and used all information required to evaluate applications against orphan designation criteria. To do so, we obtained and analyzed all 148 orphan designation review templates FDA completed as of March 2018 for designation applications it received from October to December 2017.[6] We also assessed FDA's orphan designation processes against federal internal control standards.[7] Finally, we interviewed FDA officials about the orphan designation process to determine how effectively its criteria results in consistent orphan designation determinations and how recent changes have affected their processes. To describe the characteristics of drugs seeking orphan designation, we analyzed rates of orphan designations granted and denied from January 1, 2008, to December 31, 2017, from the agency's internal database on orphan designation applications. We also analyzed information from this database on the characteristics of those drugs seeking orphan designation, such as population estimates and therapeutic areas.

To examine the orphan drugs FDA has approved for marketing, we obtained and analyzed FDA data over a 10-year period. Specifically, we identified all publicly listed orphan drugs with marketing approval dates from January 1, 2008, to December 31, 2017.[8] We then obtained and analyzed data from FDA's internal databases on the characteristics of these approved orphan drugs, including information on the time frames of each drug's FDA review, the drug's therapeutic area, and whether it was a new drug or a new use for a previously approved drug. We assessed

[6]We selected October 2017 as the beginning of this time frame, because it is when FDA implemented changes to its review template. We selected December 2017 as the end of this time frame, because FDA's review of applications received by the end of December were expected to be completed by the time of our analysis, based on the agency's timeliness goals.

[7]Internal control is a process effected by an entity's oversight body, management, and other personnel that provides reasonable assurance that the objectives of an entity will be achieved. See GAO, *Standards for Internal Control in the Federal Government*, GAO-14-704G (Washington, D.C.: Sept.10, 2014).

[8]FDA is required to make public all orphan designations it grants and also makes public all orphan drugs it has approved for marketing. It publishes the information on a website located at https://www.accessdata.fda.gov/scripts/opdlisting/oopd/, accessed November 15, 2018.

the reliability of data from FDA's internal databases on drug approvals by interviewing agency officials knowledgeable about the data, reviewing related documentation, and performing electronic data testing for obvious errors, and accuracy and completeness, where applicable. We determined that the data were sufficiently reliable for the purposes of our reporting objectives.

To describe the steps FDA has taken to address challenges in rare disease drug development, we reviewed agency guidance on rare disease drugs, such as staff training materials, and guidance on developing rare disease drugs. For example, we reviewed guidance FDA has issued in collaboration with patient advocacy groups on the experiences of patients with certain rare diseases. We also reviewed FDA studies on approved orphan drugs to identify rare disease drug development challenges, and spoke to FDA officials about how they address these challenges. To further assess rare disease drug development challenges, we identified and reviewed relevant academic research and other studies on FDA's approved orphan drugs and rare disease drug challenges. We did not independently assess the methodology or challenges identified in the academic research included in our review. We also interviewed selected industry experts and stakeholders to obtain multiple perspectives on the challenges with rare disease drug development. Specifically, we selected three industry experts with published work on FDA's orphan drug program, as well as officials from the National Organization for Rare Disorders, six individual patient advocacy groups with a rare disease focus, three pharmaceutical industry associations, and four drug manufacturers with granted orphan designations. We then categorized these challenges by thematic area.

We conducted this performance audit from October 2017 to November 2018 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

Drug manufacturers seeking to develop and receive approval to market an orphan drug go through two separate FDA processes. The drug manufacturer may first apply for orphan designation, where FDA

determines if the drug is eligible and meets the criteria for designation. The manufacturer may then apply to FDA for approval to market the orphan drug.

Orphan Designation Eligibility and FDA's Process for Granting the Designation

There are a variety of circumstances under which a manufacturer's drug is eligible for orphan designation.[9] A drug is eligible for orphan designation when it is intended to treat a disease that affects fewer than 200,000 people in the United States. A drug is also eligible for orphan designation when it is intended to treat a disease that affects 200,000 or more people in the United States and there is no reasonable expectation of recovering the cost of drug development and marketing from U.S. sales.[10] In addition, a drug that is intended to treat a specific population of a non-rare disease (known as an orphan subset) is eligible for orphan designation when a property of the drug (e.g., toxicity profile, mechanism of action, or prior clinical experience) limits its use to this subset of the population.

FDA's Office of Orphan Products Development (OOPD) administers the orphan drug program and evaluates orphan designation applications. When a drug manufacturer submits a designation application, OOPD receives and assigns it to a reviewer based on factors such as prior experience related to a particular rare disease and workload across OOPD reviewers.[11] The drug manufacturer's application is required to include such items as a description of the rare disease, documentation of the number of people affected by the disease in the United States (the population estimate), and a scientific rationale explaining why the drug may effectively treat the disease. The manufacturer can submit an orphan

[9]For drug manufacturers seeking to develop and receive FDA approval to market an orphan drug, orphan designation is a separate process from, and not a requirement for, the overall FDA drug review and approval process.

[10]Orphan designations under these circumstances have been rare. According to FDA regulations, drug manufacturers must provide an estimate for all costs incurred to develop the drug for the U.S. market, as well as 7 years of projected revenue from U.S. sales of the drug, among other things. See 21 C.F.R. § 316.21(c) (2018).

[11]OOPD also performs administrative tasks upon receiving a designation application, such as entering information into its database about the designation application (e.g., date the application was received and details about the manufacturer).

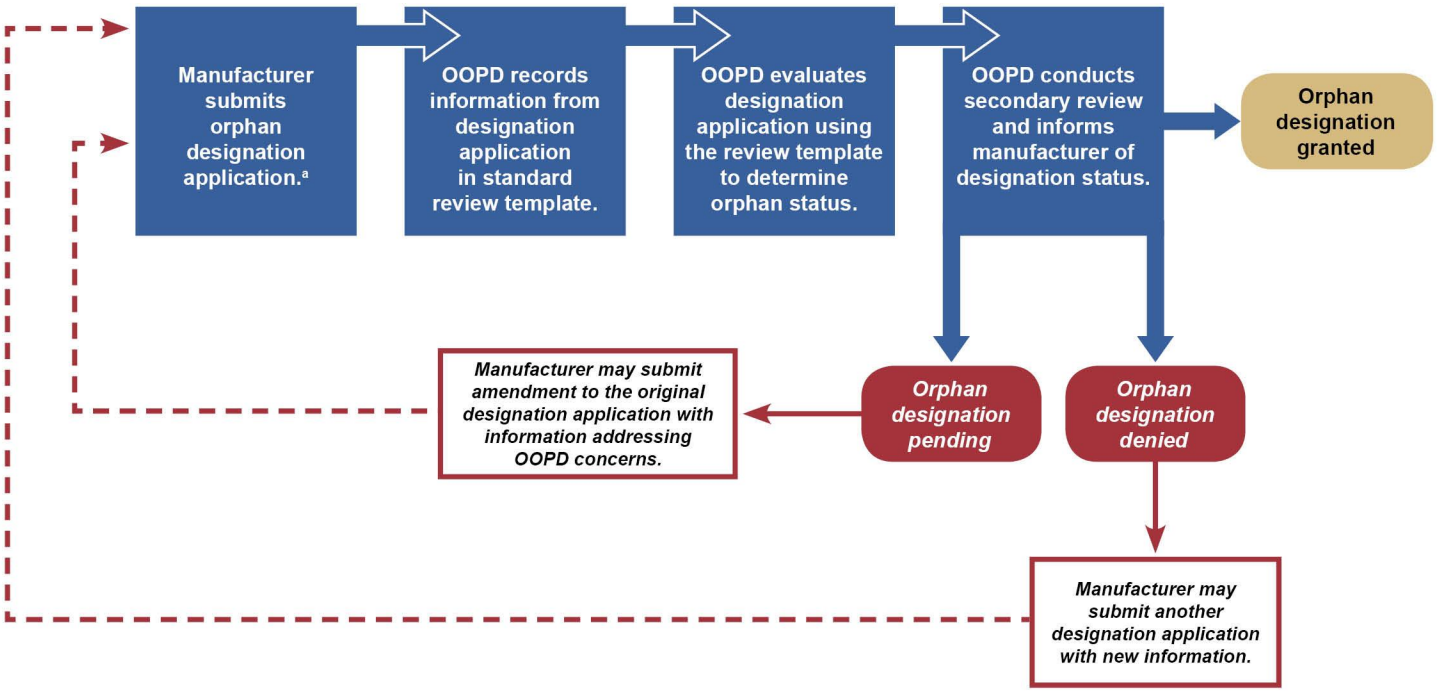
designation application at any point prior to submitting a marketing application.

When making an orphan designation decision, OOPD guidance requires reviewers to evaluate the manufacturer's application and record information about the drug and disease on a standard review template. OOPD reviewers are also expected to independently verify certain information included in the application. For example, OOPD reviewers may review independent sources to verify the population estimate provided by the manufacturer, including comparing the population estimate against prior related orphan designations.

Once the OOPD reviewer's decision is recorded on the standard review template, it undergoes a secondary review that has typically been completed by the Director of the Orphan Drug Designation Program.[12] This secondary review is intended to ensure the quality of the application review and the consistency of the review across all related designation applications. There are three possible outcomes from the designation review: (1) the orphan designation is granted, (2) the application is pending with the manufacturer due to OOPD finding it deficient, or (3) the orphan designation is denied. OOPD sends the drug manufacturer a decision letter detailing the outcome of its review. If the application is pending or denied, the decision letter describes OOPD's concerns with granting the orphan designation (e.g., insufficient evidence to support its scientific rationale) and the manufacturer may address these concerns either in an amendment to the original application (for pending status) or as a new application (for denied status). (See fig. 1.)

[12]FDA officials told us that, as of May 2018, OOPD has two secondary reviewers including the Director of the Orphan Drug Designation Program.

Figure 1: Office of Orphan Products Development's (OOPD) Orphan Designation Process



Source: GAO analysis of Food and Drug Administration documentation. | GAO-19-83

[a]OOPD follows the same process for receiving original applications and amendments to an original application.

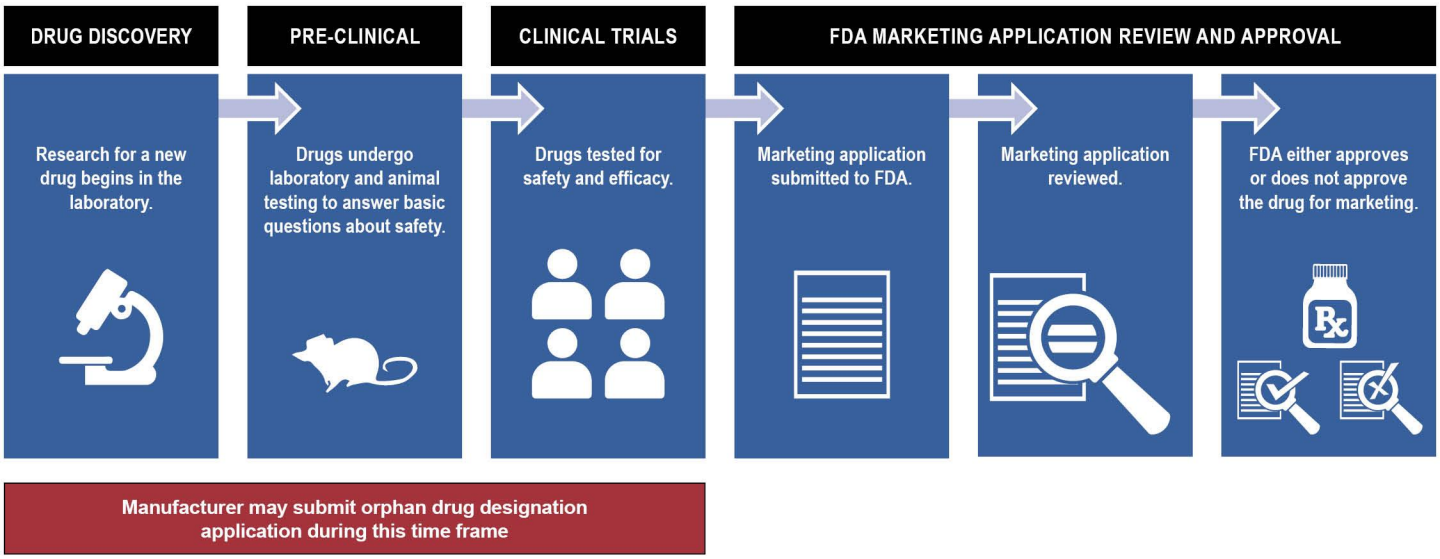
FDA's Marketing Approval Process

FDA's marketing approval process is the same for all drugs, regardless of orphan status. (See fig. 2.) Once a manufacturer has assessed the safety and efficacy of a new drug through preclinical testing and clinical trials, it may apply to FDA for approval to market the drug in the United States. To do so, a drug manufacturer submits its research in a new drug application (NDA) or biologic license application (BLA) to FDA, which then reviews and approves the drug for marketing if it is shown to be safe and effective for its intended use.[13] The two FDA centers responsible for reviewing

[13]An NDA is an application to market a new non-biologic drug—either an innovative drug or a variation of a previously marketed drug. A BLA is an application for a license to market a new biological product (generally complex drugs derived from living organisms). Manufacturers may also submit a supplement to an already approved NDA or BLA—known as an efficacy supplement—to propose changes to the way an approved drug is marketed or used, such as by adding an indication.

applications to market drugs in the United States are the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER).

Figure 2: Drug Development and FDA Marketing Approval Process Steps



Source: GAO analysis of Food and Drug Administration (FDA) documentation. | GAO-19-83

Upon completing its review of a marketing application, FDA will send an action letter with its determination to the drug manufacturer.[14] The time elapsed from the date FDA receives the application to the date it issues an action letter informing the drug manufacturer of the agency's decision is defined as one review cycle. If FDA does not approve the marketing application and the drug manufacturer resubmits the application, a new review cycle begins.

When FDA approves a drug manufacturer's marketing application, it approves the drug to treat one or more specific uses, known as indications. The approved indication is based on the clinical trial data provided in the manufacturer's marketing application and is typically narrower than the orphan designation, which is based on early drug development data for the drug's intended use in the rare disease. For example, one drug was granted orphan designation for the treatment of

[14]Agency officials told us that overall approval rates for all drugs are generally high (around 90 percent of submitted marketing applications are ultimately approved).

cystic fibrosis (the rare disease), while the drug's marketing approval was for the treatment of cystic fibrosis in patients 12 years and older who have a certain genetic mutation (the indication). The orphan drug marketing exclusivity incentive (a period of protection from competition) only applies to the drug's approved indication. OOPD determines orphan drug marketing exclusivity after receiving notification of the drug's marketing approval from CBER and CDER.

Because orphan drugs are often developed to treat patients with unmet medical needs, they may be eligible for one or more of FDA's expedited programs. FDA's four expedited programs—accelerated approval, breakthrough therapy designation, fast track designation, and priority review—are intended to facilitate and expedite the development and review of new drugs to address unmet medical needs in the treatment of a serious disease.[15] Depending on the type of expedited program, manufacturers of new drugs may receive a variety of benefits, such as additional opportunities to meet with and obtain advice from FDA officials during drug development or a shorter FDA review time goal for the marketing application.

FDA Implemented Its Modernization Plan to Address Growing Demand for Orphan Designations, and Has Recently Met Timeliness Goals

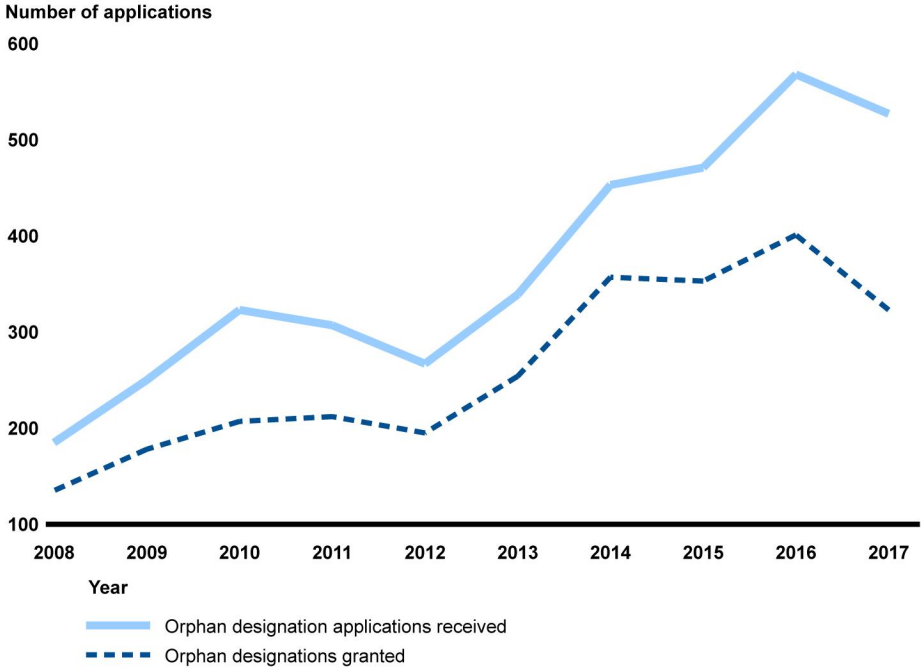
In June 2017, FDA issued its Orphan Drug Modernization Plan and has implemented a number of steps under the plan to address the demand for orphan designations.[16] According to OOPD data, the number of new designation applications received grew from 185 in 2008 to 527 in 2017 (an increase of 185 percent), while the number of designations granted

[15]In addition to these four primary expedited programs, FDA administers two other targeted expedited programs. CBER began administering the regenerative medicine advanced therapy designation program in fiscal year 2017, which is intended to facilitate the development and review of regenerative medicine therapies to address unmet medical need in those with serious conditions. As of September 2018, FDA officials told us that no drug granted regenerative medicine advanced therapy designation has been approved for marketing yet. FDA also administers the limited population antibacterial and antifungal designation program to expedite approval of certain drugs.

[16]See FDA, *Orphan Drug Modernization Plan* (June 29, 2017).

also grew during the same period. (See fig. 3.) Prior to implementing the modernization plan, OOPD had amassed a backlog of 138 applications that were pending review for more than 120 days. The modernization plan therefore established two goals: (1) eliminating the backlog of designation applications within 90 days (by September 25, 2017), and (2) ensuring that new designation applications are reviewed within 90 days of receipt.

Figure 3: Orphan Designation Applications Received and Designations Granted from 2008 to 2017, as of April 2018



Source: GAO analysis of Food and Drug Administration data. | GAO-19-83

To accomplish its first goal, the modernization plan outlined seven actions FDA planned to take to temporarily increase OOPD resources for reviewing designation applications. For example, the agency established an experienced team of senior OOPD reviewers to focus solely on the backlog of designation applications. In addition, OOPD initially enlisted temporary assistance from CBER and CDER reviewers who expressed interest in helping clear the backlog. FDA officials told us OOPD also subsequently received reviewer assistance from the Office of Medical Products and Tobacco. OOPD trained these additional reviewers on the orphan designation review process and criteria for granting orphan

status.[17] As a result of these efforts, FDA cleared the application backlog by August 28, 2017, nearly a month ahead of its goal. (See table 1 for the seven actions FDA took as part of its modernization plan to clear the designation application backlog.)

Table 1: Actions Outlined in FDA's June 2017 Orphan Drug Modernization Plan to Eliminate the Designation Application Backlog

Modernization plan action	Date implemented
Began collaboration between FDA's Office of Orphan Products Development (OOPD) and the Office of Pediatric Therapeutics to jointly review rare pediatric disease designation applications.	May 2017[a]
Transferred OOPD's role of providing secondary review of Freedom of Information Act requests to FDA's Freedom of Information Act office.	May 2017[a]
Established an experienced team of senior OOPD reviewers focused solely on addressing the backlog of designation applications.	June 2017
Implemented a pilot project to supplement OOPD reviewers with additional trained reviewers from other FDA centers to temporarily assist in addressing the backlog.	June 2017
Minimized discretionary work for all OOPD reviewers to enable them to focus on core activities.	June 2017
Tracked weekly progress in addressing backlog and reported on progress to the public.	July 2017
Developed a standard designation application review template—along with accompanying guidance for completing it—to facilitate consistent and efficient reviews of new designation applications.	October 2017

Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-19-83

[a]FDA reported that these actions, included in the Orphan Drug Modernization Plan, were implemented prior to the plan's issuance in June 2017.

To accomplish FDA's second goal of reviewing new designation applications within 90 days of receipt, the modernization plan outlined eight steps the agency planned to take to improve the efficiency of its application review process. For example, OOPD implemented a standard review template in October 2017 that it had developed under the modernization plan's first goal to address the backlog of applications. This template outlines information that reviewers are supposed to record, as applicable, from each application and evaluate when making a designation decision—namely, the (1) background information, (2) clinical superiority analysis, (3) orphan subset analysis, (4) population estimate, and (5) scientific rationale that the drug may effectively treat the

[17]Despite the ongoing demand for orphan designations, FDA officials reported that OOPD has maintained a relatively small staff dedicated to reviewing designation applications. OOPD reported that it had approximately 10.7 full-time equivalent reviewers dedicated to evaluating designation applications in the fourth quarter of 2017. According to two former OOPD Directors we spoke with, this was generally consistent with the staffing levels during their tenures, although one former Director reported that there was a period of time when OOPD had higher staffing levels.

disease.[18] (See app. I for more information about what is recorded in OOPD's review template.) The review template also includes the designation recommendation, as well as the secondary reviewer's concurrence with the designation determination. FDA officials reported that before implementing this review template, OOPD reviewers documented less-structured narrative information about each application on a prior form. In addition, OOPD introduced online training for manufacturers on the information to include in a designation application and the common issues OOPD has encountered when reviewing an application. According to officials, this training is intended to enhance the consistency and quality of designation applications, which may ultimately reduce OOPD requests for additional information from manufacturers. (See table 2 for the eight steps the agency took to improve the timeliness of its designation application review process.)

[18]The background information includes a basic description of the disease and any orphan designations granted for other drugs intended to treat the disease in the United States, among other things. A clinical superiority analysis is needed for a case where the drug is otherwise the same as an already approved drug and is for the same rare disease, but there is an explanation for why the proposed variation may be clinically superior to the first drug. A drug is considered the same as an already approved drug based on certain properties, which vary depending on whether the drug is composed of small or large molecules. OOPD does not require its reviewers to record in each review template whether a drug manufacturer is applying for orphan designation on the basis that there is no reasonable expectation of recovering the cost of drug development and marketing from U.S. sales, which is rare according to FDA officials.

Table 2: Actions Outlined in FDA's June 2017 Orphan Drug Modernization Plan to Ensure Timeliness of Designation Application Reviews

Modernization plan action	Date implemented
Reduced the Office of Orphan Products Development (OOPD) office-wide workload by, for example, reducing from a monthly to a quarterly basis the frequency of meetings of FDA's Rare Disease Council and meetings with OOPD counterparts in the European Union.	June 2017
Developed a designation review tracking report intended to help ensure that it meets timeliness goals for reviewing designation applications, and committed to providing more regular performance updates to the public.	July 2017
Undertook an organizational restructuring to maximize expertise and improve workload efficiencies.	July 2017
Established an Orphan Drug Products Policy Council to address new orphan drug issues and help ensure a consistent approach to regulating orphan drugs.	November 2017
Enhanced efficiency of orphan designation and related programs by implementing a standard designation application review template, developing online training for manufacturers to improve the quality of designation applications, and automating administrative processes, among other things.	February 2018
Streamlined OOPD's process for consulting with FDA review divisions to obtain consistent and timely information pertaining to designation reviews.	February 2018
Established a "future state" of the orphan drug program and committed to publicly reporting on its progress.[a]	February 2018
Revised its monitoring processes, modified reporting requirements, and enhanced information technology for orphan drug grant programs.	February 2018

Source: GAO analysis of Food and Drug Administration (FDA) information. | GAO-19-83

[a]FDA officials told us that the "future state" of the orphan drug program included OOPD's new manufacturer submission form for designation applications.

In July 2017, OOPD began using the new internal tracking report to monitor adherence to its 90-day timeliness goal. As of March 2018, FDA officials reported that OOPD management has received these tracking reports on a daily basis, which identify the number of days that have elapsed for each application pending review, among other things.[19] According to these tracking reports, OOPD has overall met its 90-day timeliness goal for reviewing designation applications since mid-September 2017 and has completed most application reviews within 60 days of receipt. For example, as of July 20, 2018, OOPD had 35 applications pending review for 0 to 30 days; 31 applications pending review for 31 to 60 days; 9 applications pending review for 61 to 90 days; and no applications pending review for more than 90 days.

[19]Previously, OOPD management received tracking reports on a weekly basis beginning in July 2017.

FDA Uses Consistent Criteria to Grant Orphan Designation, but Reviews Do Not Include Complete Information

FDA Generally Applies Consistent Criteria in Reviewing Applications for Orphan Designation, but Did Not Ensure that All Required Information was Appropriately Recorded or Used

OOPD applies two consistent criteria (i.e., two particular criteria that all designation applications must meet) when determining whether to grant a drug orphan status: (1) the disease that the drug is intended to treat affects fewer than 200,000 people in the United States, and (2) there is adequate scientific rationale that the drug may effectively treat the disease. For circumstances involving orphan subsets of a non-rare disease or clinical superiority, additional criteria are required for orphan designation.[20]

According to OOPD data, of the 3,690 orphan designation applications received from 2008 to 2017, OOPD determined that the majority of them met these criteria and granted them orphan status. Specifically, approximately 71 percent of applications were granted orphan designation as of April 2018. The remaining designation applications were placed in a pending status awaiting the manufacturer's response to

[20]For an orphan subset, the manufacturer must provide evidence to support that a property of the drug (e.g., toxicity profile, mechanism of action, or prior clinical experience) limits its use to a subset of a non-rare disease population. For clinical superiority, the manufacturer must provide a plausible hypothesis for why the drug provides a significant therapeutic advantage over and above that provided by the already approved drug on the basis of greater effectiveness, greater safety, or providing a major contribution to patient care.

OOPD concerns (21 percent), denied orphan designation (5 percent), or withdrawn (2 percent).[21] (See table 3.)

Table 3: Status of Orphan Designation Applications FDA Received from 2008 to 2017, as of April 2018

Orphan status	Number of designation applications	Percent of designation applications
Granted[a]	2,615	71
Pending[b]	793	21
Denied	195	5
Withdrawn[c]	87	2
Total	**3,690**	**99**

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-19-83

Note: Percent of designation applications does not sum to 100 due to rounding.

[a]For 158 of the designation applications granted orphan status, the drug manufacturer voluntarily withdrew the orphan designation, which it may do at any time. In addition, for 4 of the designation applications granted orphan status, the Office of Orphan Products Development (OOPD) withdrew the orphan designation. Although extremely rare, the agency may revoke an orphan designation in certain circumstances, including when the designation application contained false information.

[b]OOPD places designation applications in a pending status if after completing an initial review, it determines that additional information is required from the drug manufacturer to make a designation decision. For 14 of the 793 designation applications in pending status as of April 2018, the manufacturer had submitted an amended application that was under review by OOPD. For all other designation applications, the manufacturer had not submitted an amendment to the original application at the time of our review.

[c]A drug manufacturer may voluntarily withdraw a designation application at any time.

In addition, our analysis of 148 OOPD review templates completed for new designation applications received from October to December 2017 provided further detail on OOPD's designation determinations since implementing its Orphan Drug Modernization Plan. We found that for this time period, 87 designation applications (59 percent) were granted orphan status, 57 designation applications (39 percent) were placed in pending status awaiting further information from the manufacturer, and 4

[21]A drug manufacturer may voluntarily withdraw a designation application or a granted designation at any time. FDA may also revoke an orphan designation in certain circumstances, including when the designation application contained false information. According to FDA officials, the agency has revoked seven orphan designations since the ODA's enactment.

designation applications (3 percent) were denied orphan status.[22] The most common reason OOPD did not grant orphan designation was due to concerns with the adequacy of the manufacturer's scientific rationale, which occurred in 43 of the 61 pending or denied review templates.[23] OOPD reviewers noted various concerns with the scientific rationale provided in these designation applications, including that the manufacturer did not provide sufficient or adequate data to support their scientific rationale, or that the manufacturer did not provide data from the strongest available model for testing the drug.[24]

Of the five review template sections where reviewers are required to record information, we found that OOPD does not ensure that all required information is consistently recorded in the background information section and evaluated when making designation decisions. OOPD instructs reviewers to document background information, including elements of the regulatory history of the drug (e.g., U.S. and foreign marketing history), and previous orphan designations for both the drug and the disease.[25] Our analysis found that 102 of 148 OOPD review templates were missing one or more elements of the regulatory history of a drug. (See table 4.) In

[22]An application placed in pending status may be granted orphan designation if the manufacturer submits an amendment with information that sufficiently addresses OOPD concerns. Upon receiving an amendment, OOPD will complete an additional review cycle of that designation application. FDA has reported that designation applications typically undergo two review cycles. All of the 148 review templates we analyzed were for new designation applications. At the time of our review, manufacturers had submitted amendments that OOPD reviewed for 7 of 61 pending designation applications, which we included in our analysis. Four of these amended applications were granted orphan status resulting in 87 total designations, and 3 of these amended applications remained in pending status resulting in 57 total pending applications.

[23]In addition, OOPD did not grant orphan designation due to concerns with the manufacturer's population estimate in 29 designation applications, concerns with an orphan subset claim in 19 designation applications, and concerns with a clinical superiority claim in 6 designation applications. In some cases, OOPD did not grant orphan designation due to more than one area of concern with the manufacturer's designation application.

[24]According to OOPD policy, the scientific rationale is best supported by clinical data from human studies; however, in the absence of this data, manufacturers may provide data from an animal model of the disease. If human data is not available and an animal model of the disease does not exist, OOPD may consider other alternatives, such as in vitro data.

[25]According to OOPD guidance, the regulatory history for the drug is to include all U.S. and foreign marketing experience for the drug, both for orphan and non-orphan indications. The orphan designation history is to include all prior orphan designations for the disease (across all drugs) and all prior orphan applications or designations for the drug (for the disease that is the subject of the designation application).

addition, we found that 19 of 148 review templates did not capture all prior orphan designations for the drug and disease. In one case, the OOPD reviewer did not record any prior orphan designation for the disease in the review template and placed the designation application in pending status due to concerns with the manufacturer's population estimate. However, the disease that was the subject of the application had 36 related orphan designations at the time of the review, 7 of which had been granted in 2017.[26]

Table 4: Number of FDA Orphan Designation Review Templates with Complete or Missing Background Information for Applications Received From October to December 2017

Background information element required to be recorded in review template	Number of review templates	
n/a	Complete information	Missing information
Regulatory history[a]	44	102[b]
Regulatory history[a]: U.S. marketing history	98	48
Regulatory history[a]: Foreign marketing history	84	62
Regulatory history[a]: Active investigational new drug applications[c]	109	37
Regulatory history[a]: Adverse actions[d]	52	94
Orphan designation history of drug and disease[e]	94	19

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-19-83

[a]In some cases, Office of Orphan Products Development (OOPD) review templates were missing more than one element of the regulatory history.

[b]For one review template, we could not determine whether the regulatory history for the drug was complete due to an unclear template. In another case, the OOPD reviewer noted that the regulatory history was missing from the designation application and requested it from the manufacturer.

[c]Manufacturers submit an investigational new drug application to FDA prior to commencing clinical trials for a drug. This application summarizes the data that have been collected on the drug and outlines plans for clinical trials.

[d]According to FDA officials, adverse actions include any regulatory actions taken against the drug, such as denying orphan designation or marketing approval.

[e]For 35 review templates, we were unable to determine whether the OOPD reviewer captured all relevant prior orphan designations.

According to FDA officials, although the background information required in the review template may not directly affect a designation decision, it provides important context that is critical to ensuring a complete review of a designation application. For example, FDA officials told us that in cases where the designation application is for a disease with little published

[26]The drug that was the subject of this designation application ultimately obtained orphan designation in May 2018.

information available, it may help to know the drug's U.S. marketing history to identify whether CBER or CDER has experience with the disease.[27] Additionally, the prior orphan designation history can help the OOPD reviewer identify previously accepted methodologies to estimate the population for a disease.

Despite requiring its reviewers to record background information for each designation application, OOPD's guidance does not provide instructions on how to use this information when evaluating the applications. Internal control standards for the federal government specify that agencies should record relevant, reliable, and timely information, and process that information into quality data that enables staff to carry out their responsibilities.[28] Without instructions on how to use the background information required in its review templates, OOPD reviewers may not consistently use all of the information needed to conduct a complete evaluation of a designation application.

Additionally, OOPD instructs its reviewers to consider evidence found in independent sources to verify the population estimate provided in a designation application. However, in 23 of 148 OOPD review templates, reviewers did not include the results of any such independent verification in their evaluation of the manufacturer's population estimate.[29] Internal control standards state that agencies should conduct checks of their recorded data to ensure its accuracy and completeness, but we found that OOPD does not fully conduct such data checks. Without ensuring that its reviewers conduct and record the results of independent verification of population estimates, OOPD cannot be assured that quality information is consistently informing its designation determinations.

For the 148 templates we reviewed, we found that OOPD granted orphan designation to 26 applications missing required information. Specifically,

[27]According to FDA officials, OOPD reviewers may consult with CBER or CDER reviewers if they have specific medical questions about the disease or drug that is the subject of a designation application.

[28]See GAO-14-704G.

[29]OOPD assigns designation applications to reviewers, in part, based on prior experience with the disease that is the subject of the request. As such, it may be the case that for some or all of these 23 review templates, OOPD reviewers were familiar with the population for these diseases and determined that no further independent verification was needed. However, there was no documentation to confirm that reviewers made this determination.

we found that OOPD granted designation to 11 applications where the reviewer did not record prior orphan designation history, to 13 applications where the reviewer did not document independent verification of the manufacturer's population estimate, and to 2 applications where the reviewer did neither. In cases where the background information was incomplete or there was no documentation of independent verification of the manufacturer's population estimate, there also was no evidence that the secondary reviewer verified the completeness of these sections of the review templates.

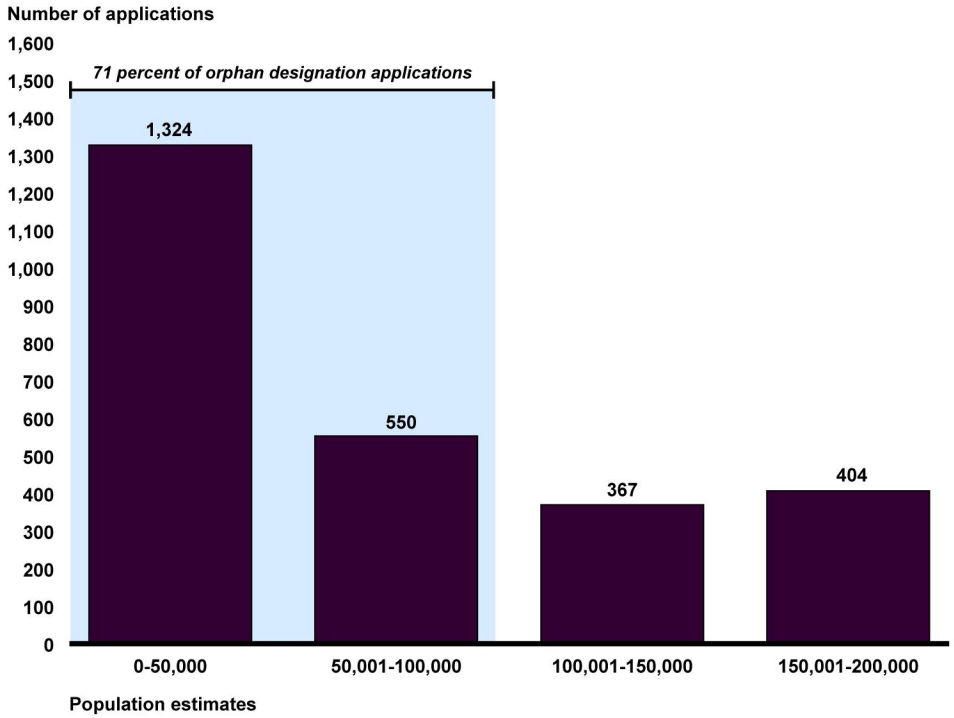
Most Orphan Designation Applications Had a Population Estimate of Fewer than 100,000 and Over Half of the Applications Target One of Four Therapeutic Areas

Approximately 71 percent of orphan designation applications received by FDA from 2008 to 2017 were for drugs intended to treat diseases affecting 100,000 or fewer people.[30] In addition, half of the applications received during this time frame were for drugs intended to treat populations of 50,000 or fewer people. (See fig. 4.) For applications that OOPD granted orphan designation, the population estimates for the diseases they were intended to treat ranged from 0 to 199,966 people.[31]

[30]OOPD's database included a population estimate for 2,659 of 3,690 designation applications it received from 2008 to 2017. FDA officials reported that a population estimate is routinely recorded in OOPD's database only for designation applications that are granted orphan status. OOPD reviewers are not required to enter a population estimate into the database for designation applications that are placed in pending status or denied designation.

[31]Designation applications with very small population estimates were for the treatment of diseases that are extremely rare in the United States (e.g., Krabbe disease, an inherited genetic disease that destroys the protective coating of nerve cells in the brain and nervous system, and affected an estimated 86 people in the United States), and of viruses (e.g., Ebola virus) or hazards (e.g., acute radiation), where there was no exposure in the United States at the time of the designation application.

Figure 4: Number of Orphan Designation Applications from 2008 to 2017, by Population Estimate



Source: GAO analysis of Food and Drug Administration data. | GAO-19-83

Notes: This figure includes population estimates for 2,645 designation applications that were either granted orphan status or placed in pending status. Two pending designation applications not included in the figure had populations greater than 200,000 and were pending a response from the manufacturer as of April 2018. In addition, Office of Orphan Products Development data had 6 designation applications that were denied orphan designation and 6 applications that were withdrawn.

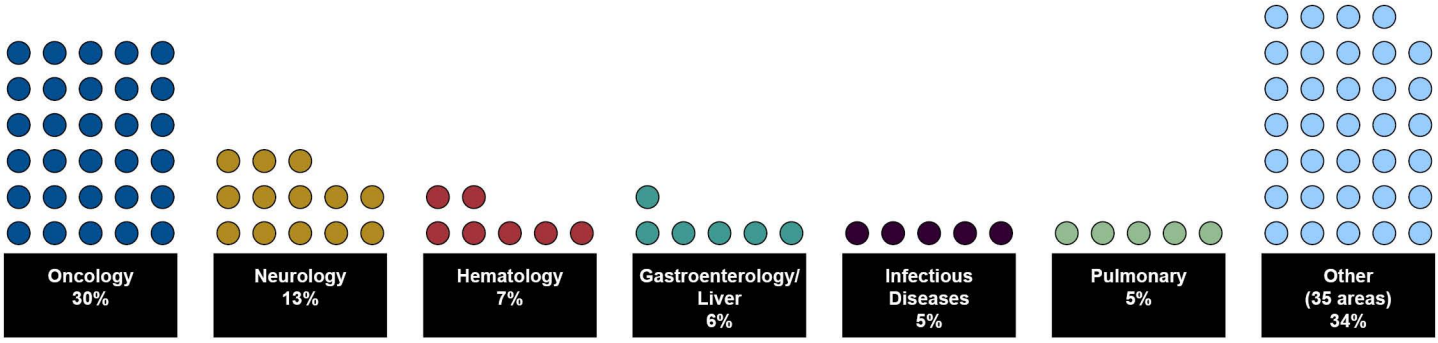
Designation applications for drugs intended to treat a disease affecting zero people were for viruses (e.g., Ebola virus) or hazards (e.g., acute radiation), where there was no exposure in the United States at the time of the designation application.

Of 3,491 orphan designation applications OOPD received from 2008 to 2017, over half were for the therapeutic areas of oncology (30 percent), neurology (13 percent), hematology (7 percent), and gastroenterology and liver (6 percent).[32] Thirty-seven other therapeutic areas accounted for the remaining 44 percent of applications, with each therapeutic area accounting for 5 percent or fewer of designation applications received

[32]OOPD received a total of 3,690 designation applications from 2008 to 2017, of which 199 did not have a therapeutic area captured in OOPD's internal database.

during this time frame. Some of these other therapeutic areas included pulmonary, immunology, cardiology, and dermatology. (See fig. 5.)

Figure 5: Therapeutic Areas of Orphan Designation Applications FDA Received from 2008 to 2017



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-19-83

Note: This figure represents the 3,491 (of 3,690) applications received from 2008 to 2017 with a therapeutic area captured in the Office of Orphan Products Development's internal database.

Additionally, our analysis of 148 OOPD review templates from October to December 2017 found that

- 29 applications (20 percent) requested orphan status based on an orphan subset claim, 7 of which were granted orphan designation; and
- 7 applications (5 percent) requested orphan status based on a clinical superiority claim, 2 of which were granted orphan designation.[33]

[33]Since OOPD did not consistently track certain orphan designation characteristics, and therefore does not have reliable data for the characteristics, we used review template information for these characteristics instead of OOPD's application data from 2008 to 2017. All review templates we analyzed were for designations requested on the basis of treating a rare disease (or an orphan subset of a non-rare disease). None requested designation on the basis that there is no reasonable expectation of recovering the cost of drug development and marketing from U.S. sales.

FDA's Orphan Drug Marketing Approvals Increased from 2008 to 2017, Were Focused in Two Therapeutic Areas, and Typically Required about 9 Months for Agency Review

FDA approved 351 orphan drugs for marketing from 2008 to 2017. Orphan drug marketing approvals have increased over this period, from 17 in 2008 to 77 in 2017, and have accounted for an increasing proportion of all FDA marketing approvals.[34] Orphan drug marketing approvals also vary by certain characteristics, but were typically in one of two therapeutic areas and required about 9 months for FDA review, among other commonalities.

Therapeutic area. From 2008 to 2017, 53.3 percent of orphan drug marketing approvals were in one of two therapeutic areas that were also common for granted designations: oncology (42.5 percent) and hematology (10.8 percent). There were 27 different therapeutic areas overall, with 7 of those areas having 10 or more approved orphan drugs. (See app. II for FDA's orphan drug marketing approvals from 2008 to 2017 by therapeutic area.)

Number of indications. Of the 351 orphan drug marketing approvals from 2008 to 2017, there were 252 unique drugs, because drugs can be approved for more than one orphan indication. For example, the oncology drug Velcade received FDA approval in 2008 as a first-line therapy for multiple myeloma, and received approval for a second indication in 2014 for treatment of mantle cell lymphoma if the patient has not received at least one prior therapy. (See app. II.) The majority of drugs had one orphan indication (77.4 percent) or two orphan indications (15.9 percent). However, several drugs (6.7 percent) were approved to treat three or more orphan indications. Two oncology drugs had the most approved

[34]We previously reported that orphan drugs as a share of all marketing approvals grew from 5 percent in 2005 to 21 percent in 2016. See GAO, *Drug Industry: Profits, Research and Development Spending, and Merger and Acquisition Deals,* GAO-18-40 (Washington, D.C.: Nov. 17, 2017). According to OOPD data, 7 percent of 2,615 orphan designations granted from 2008 to 2017 resulted in an orphan drug marketing approval.

orphan indications: Imbruvica (10 orphan indications) and Avastin (9 orphan indications).[35]

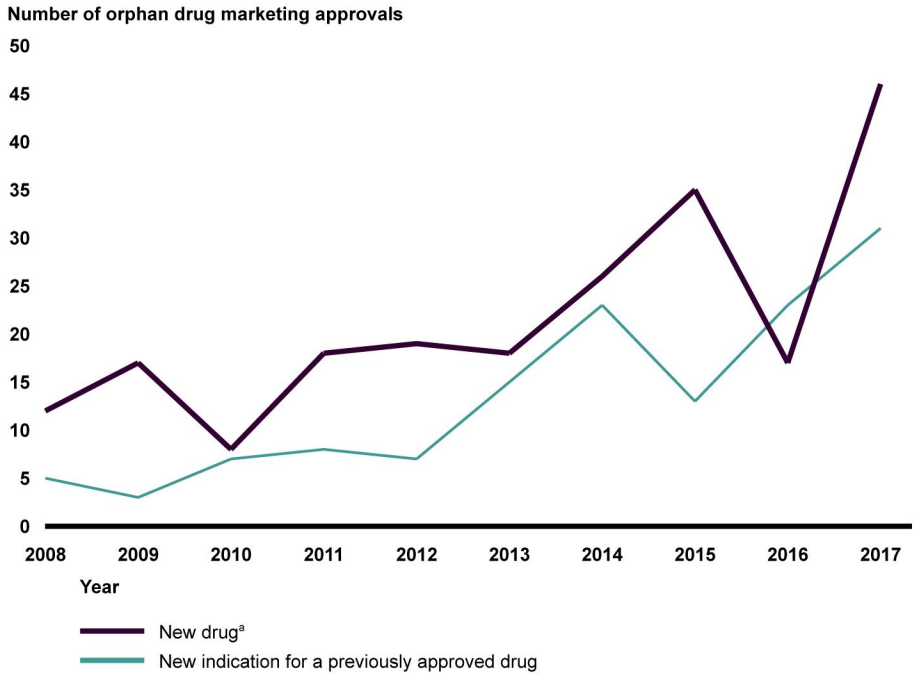
New drug or new indication for previously approved drug. The majority (61.5 percent) of orphan drug marketing approvals from 2008 to 2017 have been for a new drug not previously approved for any use, while the remainder (38.5 percent) have been for a new indication for a drug previously approved to treat a rare or non-rare disease.[36] (See fig. 6.) Of the new orphan drugs that received marketing approval, the majority have been for novel uses—new molecular entities or new therapeutic biologics that are often innovative and serve previously unmet medical needs, or otherwise significantly help to advance patient care and public health.[37]

[35]In an October 2017 presentation that analyzed 451 unique orphan drug approvals from 1983 to 2016, FDA reported that 83 percent of approvals were originally for the orphan indication. The remaining drugs were either originally approved for a non-orphan indication (12 percent), approved for both orphan and non-orphan indications (3 percent), or were approved prior to the ODA (2 percent).

[36]For example, FDA approved the drug Humira to treat five orphan indications from 2008 to 2016 in the areas of dermatology, gastroenterology, ophthalmology, and rheumatology. Humira also has FDA marketing approval for non-orphan diseases such as rheumatoid arthritis. FDA data on orphan drug marketing approvals did not allow us to systematically analyze the orphan and non-orphan indications for previously approved drugs.

[37]Orphan drugs as a share of all novel drug approvals ranged from 22 percent in 2007 to 42 percent in 2015. See GAO-18-40.

Figure 6: Number of Orphan Drug Marketing Approvals by New Drug or New Indication, 2008 to 2017



Source: GAO analysis of Food and Drug Administration data. | GAO-19-83

[a]A new drug approval can be for a "novel" use (a new molecular entity or new therapeutic biologic that is often innovative and serves previously unmet medical needs, or otherwise significantly helps to advance patient care and public health).

FDA review time. For orphan drug marketing approvals from 2008 to 2017, the median time from FDA receiving a marketing application to approval was about 9 months, and ranged from 75 days to about 17 years.[38] FDA averaged about 1.2 review cycles for these drugs, with the

[38]The length of the FDA review time for the orphan drug approval that took 17 years was due, in part, to the timing of the drug manufacturer's response to FDA after a first review. After FDA sent a non-approval letter for the initial marketing application in January 1992, the manufacturer did not submit its complete response until July 2007, and the drug subsequently received FDA approval in March 2008. According to FDA data, 8.3 percent of orphan drugs from 2008 to 2017 took more than 2 years from the initial marketing application receipt date to the marketing approval date.

number of cycles ranging from one to four reviews.[39] Two neurology drugs each had the largest number of reviews (four).

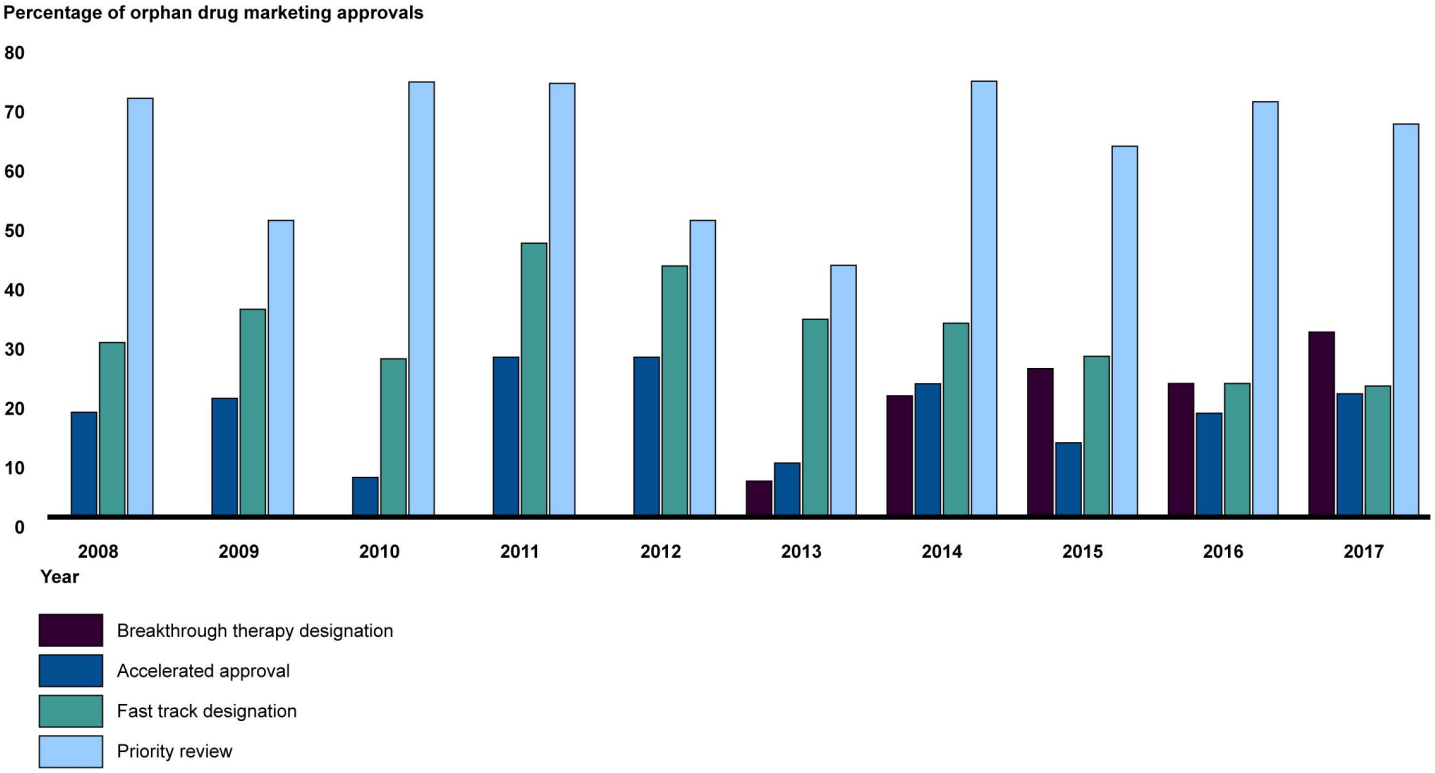
Expedited programs. Approximately 71 percent of orphan drug marketing approvals from 2008 to 2017 benefitted from at least one type of FDA's four primary expedited programs (accelerated approval, breakthrough therapy designation, fast track designation, or priority review).[40] Most orphan drug approvals in each year received priority review, while less than half received accelerated approval, breakthrough therapy designation, or fast track designation in the year the drug was approved.[41] (See fig. 7.) Very few (six) orphan drug approvals were granted all four of these expedited programs in the year approved.

[39]One review cycle is the time elapsed from the date FDA receives the application to the date it issues an action letter informing the drug manufacturer of the agency's decision. If FDA does not approve the marketing application and the drug manufacturer resubmits the application, a new review cycle begins.

[40]FDA officials told us that a number of drugs granted orphan designation have also benefitted from FDA's newer expedited program for regenerative medicine advanced therapy designation (17 of 26 granted designations), but no drug granted this newer designation has been approved for marketing, as of September 2018. FDA also administers the limited population antibacterial and antifungal designation program to expedite approval of certain drugs.

[41]An orphan drug may be eligible for one or more of these expedited programs, which are intended to facilitate and expedite the development and review of new drugs to address unmet medical needs in the treatment of a serious disease.

Figure 7: Percent of Orphan Drugs Benefitting from Each Type of FDA Expedited Program in Year Approved, 2008 to 2017



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-19-83

Note: An orphan drug may be eligible for one or more of FDA's four primary expedited programs—accelerated approval, breakthrough therapy designation, fast track designation, and priority review. These programs are intended to facilitate and expedite the development and review of new drugs to address unmet medical needs in the treatment of a serious disease. The breakthrough therapy designation was established in July 2012 and the first breakthrough therapy designations were made in 2013.

FDA Issued Guidance and Offered Training to Address Ongoing Rare Disease Drug Development Challenges

FDA Developed Guidance and Training to Better Inform Its Reviewers and the Public about Rare Disease Drug Development Challenges

To address rare disease drug development challenges, FDA has established guidance for internal and public use, and offered training to its reviewers. FDA's guidance and training on rare diseases includes topics related to more general drug development issues, as well as the agency's marketing approval process as it applies to orphan drugs.

In general, FDA's review centers—CBER and CDER—are responsible for establishing guidance on general rare disease drug development issues.[42] For example, FDA published draft guidance for industry in August 2015 on common issues in rare disease drug development.[43] The guidance discusses important aspects of drug development, such as the need for an adequate understanding of the natural history of the disease and the drug's proposed mechanism of action, and the standard of evidence to establish safety and effectiveness. CBER published additional draft guidance in July 2018 on rare disease drug development specific to gene therapy in order to help manufacturers consider issues such as limited study population size, safety issues, and outcomes.[44]

[42]CDER has a Rare Diseases Program that, among other things, coordinates its policy, procedures, and training for reviewing rare disease treatments, and collaborates with external and internal stakeholders to promote the development of rare disease treatments. CBER has a Rare Disease Liaison to coordinate the center's rare disease activities, including working with CDER, OOPD, and external stakeholders.

[43]FDA, *Rare Diseases: Common Issues in Drug Development, Guidance for Industry* (Rockville, Md.: August 2015).

[44]FDA, *Human Gene Therapy for Rare Diseases, Draft Guidance for Industry* (Rockville, Md.: July 2018).

FDA has also conducted studies to understand rare disease drug development challenges. In March 2011, FDA issued a report to Congress on the strengths and weaknesses of its regulatory process with respect to rare and neglected tropical diseases.[45] In that report, a group of expert FDA officials found that its regulations allowed experienced reviewers to use flexibility and scientific judgment in determining the safety and efficacy of rare disease drugs. However, the group also noted areas for improvement, such as the need to develop training for FDA reviewers and to increase communication efforts with stakeholders, including industry and advocacy organizations.

One other key area the group identified was the need to analyze the agency's orphan drug marketing approvals to further understand the factors helping or hindering drug development. To do so, FDA analyzed a subset of orphan drug approvals and published two studies:

- FDA's February 2012 publication on rare disease drug approvals between 2006 and 2011 found that substantial proportions of marketing approvals were for innovative drugs, and most clinical studies were highly unique in terms of the study design, controls, and outcome measures used.[46] FDA concluded that developing defined policy and consistency around such diverse drugs and unique clinical studies would be difficult.
- FDA's May 2012 publication on marketing applications between 2006 and 2010 concluded that, due to the high approval rates for applications targeting rare diseases in its study, increased efforts in the agency's review process would be unlikely to substantially increase the number of new rare disease drugs.[47]

FDA's patient engagement programs have also focused on rare disease drug development. As of February 2016, the agency reported that nearly half of patient-focused drug development meetings—meetings to obtain the patient perspective on specific diseases and their treatments—have been focused on rare diseases. In addition, four of six patient advocacy groups we interviewed said that they used this type of meeting or another

[45]FDA, *Report to Congress: Improving the Prevention, Diagnosis, and Treatment of Rare and Neglected Diseases* (March 2011).

[46]A.R. Pariser and L.J. Bauer, "Therapeutics for Rare Disease Indications and the U.S. FDA: What are the facts?" *Global Forum*, vol. 4, issue 1 (February 2012).

[47]A.R. Pariser, et. al., "Characteristics of Rare Disease Marketing Applications Associated with FDA Product Approvals 2006-2010," *Drug Discovery Today* (May 2012).

structured meeting to provide FDA input on their rare disease. One patient advocacy group told us that its meeting with FDA helped lead to issued guidance on drug development for Duchenne muscular dystrophy.[48]

As part of its efforts to better inform reviewers about the agency's regulatory framework and drug development challenges with respect to rare diseases, FDA has developed a training course and holds an annual all-day meeting for reviewers. (See table 5.) In its rare disease training course, FDA describes its authority to be flexible in reviewing marketing applications for rare disease drugs. Multiple studies found that FDA has regularly used this flexibility in approving rare disease therapies; for example, by allowing marketing approval based on one adequate and well-controlled study, rather than requiring two.[49]

[48]See FDA, *Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment: Guidance for Industry* (Rockville, Md.: June 2015).

[49]For example, see National Organization for Rare Disorders, *Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Cataloguing FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders* (2011). The Food, Drug, and Cosmetic Act requires new drug applications to provide substantial evidence of the drug's effectiveness through adequate and well-controlled investigations. See 21 U.S.C. § 355(d). FDA generally requires two adequate and well-controlled investigations to support a new drug application.

Table 5: Food and Drug Administration (FDA) Rare Disease Training for Its Reviewers

FDA training	Description
Rare disease 101 web-based course	FDA's Center for Drug Evaluation and Research (CDER), in collaboration with the Office of Orphan Products Development (OOPD) and the Center for Biologics Evaluation and Research (CBER), developed a course to educate new and experienced staff about the basic concepts of rare disease drug development and review. FDA officials told us this web-based course is available to FDA staff on-demand. The training includes the following four learning modules. 1. Special challenges of rare diseases and the Orphan Drug Act. 2. Efficacy evidence. 3. Safety evidence. 4. Resources for FDA reviewers.
Annual rare disease drug development meeting	FDA convenes an annual full-day meeting to provide training for reviewers and other staff from CBER, CDER, and OOPD. Each rare disease meeting has a theme and may include patient advocacy groups and industry speakers: • The May 2016 meeting was titled "Connecting the Stakeholders," and featured presentations from patient advocacy groups, a drug manufacturer, and other federal agencies. • The May 2017 meeting was titled "Strategies for Small Clinical Trials," and featured presentations from FDA and a patient advocacy group on topics such as successful case studies and safety concerns. • The May 2018 meeting was titled "Emerging Topics in Rare Diseases," and featured presentations from FDA on programmatic updates and applying flexible review approaches.

Source: GAO analysis of FDA information. | GAO-19-83

Stakeholders and Research Identified Ongoing Rare Disease Drug Development Challenges, while Opinions on the Orphan Drug Act Incentives Varied

Stakeholders we interviewed, including industry experts and patient advocacy groups, and research we reviewed identified general rare disease drug development challenges, as well as more specific concerns pertaining to the ODA incentives and pricing. However, opinions of some of the concerns attributed to the ODA incentives varied among stakeholders.

Barriers to rare disease drug development. The two barriers to rare disease drug development most commonly cited among stakeholders we interviewed were (1) the need for more basic scientific research (e.g., understanding patient experiences and progression of symptoms, known as a disease's natural history), and (2) the difficulty in recruiting small populations for clinical trials. One drug manufacturer explained that, when a disease affects a small population, it is hard to identify and recruit participants, because they may be geographically dispersed or have to

travel long distances to participate in the trial. Identifying these participants and enrolling them into a clinical trial is therefore both labor- and resource-intensive.

A number of studies conducted by FDA and others identified similar challenges, as well as other rare disease drug development issues.[50] For example, a 2010 study by the National Academies of Science, Engineering, and Medicine noted that researchers still lack a basic understanding of the mechanisms that underlie many rare diseases. Another drug development challenge identified in the study is attracting trained investigators to study rare diseases.

To address some of these challenges, OOPD has a number of grant programs focused on rare disease drug development, including one that funds studies that track the natural history of a disease over time to identify demographic, genetic, environmental, and other variables that may lead to drug development. In addition, FDA's fiscal year 2019 budget justification includes a request for funds to develop clinical trial networks to create an understanding of the natural history and clinical outcomes of rare diseases.

Significance of ODA incentives in fostering drug development. Although many stakeholders we spoke with categorized the ODA's incentives as significant to rare disease drug development, two stakeholder groups we spoke with—industry experts and drug manufacturers—largely categorized the incentives as less important than did other stakeholders. For example, two of four drug manufacturers we interviewed told us that their company's drug development decisions are based on the disease areas it wants to target and not due to ODA incentives. In addition, several stakeholders noted non-ODA drivers of orphan drug growth, including the ability to command high prices and advances in scientific discovery for some rare diseases.

Several studies also noted limitations of the ODA incentives, including the structure of the orphan drug tax credit, the decreasing impact of the marketing exclusivity incentive in protecting orphan drugs from

[50]For example, see FDA, *Report to Congress: Improving the Prevention, Diagnosis, and Treatment of Rare and Neglected Diseases* (March 2011); National Academies of Science, Engineering, and Medicine, *Rare Diseases and Orphan Products: Accelerating Research and Development* (Washington, D.C.: 2010); and I. Melnikova, "Rare Diseases and Orphan Drugs," *Nature Reviews*, vol. 11 (April 2012).

competition, and the ability of the incentives to target "truly" rare conditions that would not otherwise have obtained sufficient investment.[51] For example, the Congressional Research Service reported in December 2016 that the benefits of the orphan drug tax credit are limited to companies with positive tax liabilities. As a result, the Congressional Research Service concluded that the typical small startup company investing in the development of an orphan drug may be unable to take advantage of the tax credit during its first few years of operation when its expenses exceed its revenue and cash flow may be a problem.

Certain circumstances under which drug manufacturers may obtain ODA incentives. Several stakeholders we spoke with were critical of how drug manufacturers may obtain ODA incentives, such as for drugs that were already approved to treat another disease or for multiple orphan designations for the same drug. For example, one industry expert argued that granting multiple orphan designations for the same drug subverts the purpose of the ODA to support development of drugs that may not otherwise be profitable, as a drug manufacturer can make a return on investment from the drug from multiple patient groups rather than just one. In contrast, many patient advocacy groups we spoke with noted that drug manufacturers' ability to obtain ODA incentives under certain circumstances, such as multiple orphan designations for the same drug, are needed for further investment in drug development. In particular, they noted that this provides an incentive for manufacturers to demonstrate their drugs are safe and effective for individuals who have a rare disease (particularly for FDA-approved drugs with an unapproved use—known as off-label use) and account for any differences within rare diseases.

A number of studies raised similar concerns about these and other issues, including off-label use of orphan drugs.[52] Specifically, one study

[51]For example, see Congressional Research Service, *Tax Expenditures: Compendium of Background Material on Individual Provisions* (Washington, D.C.: December 2016); A. Sarpatwari, et. al., "Evaluating the Impact of the Orphan Drug Act's Seven-Year Market Exclusivity Period," *Health Affairs*, vol. 37, no. 5 (May 2018); and J.H. Döring, et. al., "Thirty Years of Orphan Drug Legislation and the Development of Drugs to Treat Rare Seizure Conditions: A Cross Sectional Analysis," PLoS ONE (Aug. 24, 2016).

[52]For example, see O. Wellman-Labadie and Y. Zhou, "The US Orphan Drug Act: Rare Disease Research Stimulator or Commercial Opportunity?" *Health Policy,* vol. 95 (2010); M.G. Daniel, et. al., "The Orphan Drug Act: Restoring the Mission to Rare Diseases," *American Journal of Clinical Oncology*, vol. 39, no. 2 (April 2016); and A.S. Kesselheim, C.L. Treasure, and S. Joffe, "Biomarker-Defined Subsets of Common Diseases: Policy and Economic Implications of Orphan Drug Act Coverage," *PLoS Med,* vol. 14, no. 1 (January 2017).

noted that, due to increasing investment in precision medicine, manufacturers may develop drugs treating a particular genetic subset of a non-rare disease. These subsets may qualify for ODA incentives, even though they may not face the same development challenges as “true” rare diseases. For example, three orphan drugs were approved as treatments for a subset of non-small cell lung cancers that have a specific gene mutation. According to the study, these drugs can also be used off-label for diseases other than the non-small cell lung cancer subset for which they were originally approved.

FDA has taken steps in recent years to address certain circumstances under which drug manufacturers may obtain orphan designation. For example, the agency recently issued guidance stating that it no longer plans to grant orphan designation to pediatric subsets of non-rare diseases. The agency attributed its decision, in part, to a loophole that could result in a drug receiving an orphan designation for a pediatric subset being exempt from requirements under the Pediatric Research Equity Act to study drug safety and effectiveness in pediatric subpopulations.[53] FDA also held a workshop in May 2018 to seek input on appropriate orphan designation for certain oncology treatments to stay current with evolving knowledge.

Orphan drug pricing. Stakeholders we interviewed and research we identified also raised concerns about the high prices drug manufacturers can charge for orphan drugs when receiving ODA incentives.[54] Several stakeholders we spoke with noted that it was difficult to discuss the ODA without addressing concerns with how orphan drugs are priced. For

[53]See FDA, *Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases: Guidance for Industry* (Silver Spring, Md.: July 2018). FDA had historically granted orphan designation to pediatric subsets of non-rare diseases as a way to foster research in pediatric populations. However, the Pediatric Research Equity Act, which was enacted after the ODA, requires that certain marketing applications contain an assessment of safety and effectiveness for the proposed indication in all relevant pediatric subpopulations, but exempted indications with an orphan designation from this requirement. Because the pediatric subpopulation designation does not mandate that manufacturers conduct such studies, this resulted in a way for manufacturers to avoid conducting such studies.

[54]For example, see EvaluatePharma, *Orphan Drug Report 2018* (May 2018). EvaluatePharma reports that, of the top 100 drugs by sales in the United States, the average cost per patient per year for an orphan drug was $147,308 in 2017, compared with $30,708 for a non-orphan drug. In addition, worldwide orphan drug sales are forecast to grow at a rate of 11.3 percent from 2018 to 2024, double the rate forecast for the non-orphan drug market.

example, one patient advocacy group told us that it may be appropriate for a drug to receive multiple orphan designations, but that the drug manufacturer should revise the price of its drug to reflect the number of orphan designations. Several studies have also pointed to high orphan drug prices as a public health challenge in terms of access and affordability, particularly when orphan drug development may be less costly than non-orphan drugs due to smaller and fewer efficacy and safety trials, shorter FDA review time, higher marketing approval success rates, and lower marketing costs.[55] One study found an inverse relationship between the price of orphan drugs and their volume of use (i.e., the more expensive the orphan drug, the fewer patients who use the drug), and noted that over the past 20 years spending on medicine in the U.S. market has shifted increasingly toward drugs that treat relatively few people, such as those with rare diseases.[56]

Conclusions

With significant unmet need for most rare diseases, the ODA provides manufacturers with a variety of incentives if they develop drugs that meet orphan designation criteria. To ensure that drug manufacturers' claims in their orphan designation applications are accurate, FDA must conduct thorough and consistent evaluations. FDA took several steps beginning in June 2017 to improve the consistency and efficiency of these evaluations, including introducing a standard review template and guidance for completing it. However, we found that FDA does not always ensure that all information is consistently recorded in its review templates and evaluated when making designation determinations, which are critical steps needed to understand the full context of a drug's intended use in the rare disease. FDA has a number of options it could take to ensure that reviewers obtain all necessary information and use it to inform orphan designation determinations. For example, we found that FDA's guidance was not always clear in instructing reviewers how they should use the information they record. Clarifying these requirements in

[55]For example, see Department of Health and Human Services, *Report to Congress: Prescription Drugs: Innovation, Spending, and Patient Access* (Dec. 7, 2016); National Academies of Science, Engineering, and Medicine, *Making Medicines Affordable: A National Imperative* (Washington, D.C.: 2017); and K. Mikami, "Orphans in the Market: The History of Orphan Drug Policy," *Social History of Medicine* (2017).

[56]See IQVIA Institute for Human Data Science, *Orphan Drugs in the United States: Growth Trends in Rare Disease Treatments* (October 2018).

guidance could help reviewers make use of this information, including the secondary reviewers who ensure the consistency and quality of designation reviews. While FDA action to improve its designation reviews will not address the broader rare disease drug development challenges identified by stakeholders we interviewed and research we analyzed, it could help FDA ensure the consistency of its review process, particularly as demand for orphan designations continues to grow.

Recommendation for Executive Action

We are making the following recommendation to FDA:

The Commissioner of FDA should ensure that information from orphan drug designation applications is consistently recorded in OOPD review templates and evaluated by OOPD reviewers when making an orphan designation decision. (Recommendation 1)

Agency Comments

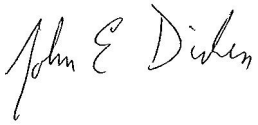
We provided a draft of this report to the Department of Health and Human Services (HHS) for comment. In its written comments, reproduced in appendix III, the agency concurred with our recommendation. HHS also provided technical comments, which we incorporated as appropriate.

In its response, HHS stated that it would consider our recommendation as part of FDA's ongoing efforts to evaluate and revise the designation review template, and to train reviewers. Regarding the background information in the review template, HHS also noted that many drugs requesting orphan designation do not have relevant regulatory history, particularly adverse actions, as these drugs are early in drug development at the time of requesting orphan designation. However, HHS agreed with the importance of consistently documenting and utilizing background information, and stated that FDA will continue to apply consistent criteria to its review decisions.

We are sending copies of this report to the Secretary of Health and Human Services, appropriate congressional committees, and other interested parties. The report is also 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 us at (202) 512-7114 or dickenj@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs are on the last page of this report. GAO staff who made major contributions to this report are listed in appendix IV.

Sincerely yours,



John E. Dicken
Director, Health Care

Appendix I: Information Recorded in OOPD's Standard Designation Review Template

In October 2017, the Food and Drug Administration's Office of Orphan Products Development (OOPD) introduced a standard review template, along with guidance for how to complete it, to aid its reviewers in evaluating orphan designation applications. OOPD guidance instructs its reviewers to record information about the drug and disease on the standard review template, as well as the results of independent verification done for certain information included in the application. The template is then used with the designation application to determine whether to grant orphan designation to a drug. (See table 6 for the information recorded in OOPD review templates.)

Table 6: Office of Orphan Products Development (OOPD) Guidance for Recording Information in Its Designation Application Review Template

Review template section	Description of information recorded
Background information: Date of original application	The date of the original designation application, including the date the application was received by FDA.
Background information: Date(s) of amended application(s)	The date(s) of any amendment to the original designation application, including the date(s) that FDA received the amendment.
Background information: Date review completed	The date that initial review of the designation application was completed.
Background information: Designation number	The number identifier assigned by OOPD for the designation application.
Background information: Prior or related designation number	Any prior or related designation number(s) for the designation application (e.g., if the designation application is related to a prior designation application in pending status for over a year).
Background information: Chemical name	A description of the molecular structure of the drug.
Background information: Generic name	Generic name for the drug (if available) or the name of its active ingredient.
Background information: Other (code) name	Any other name used for the drug.
Background information: Manufacturer	Name and address of the manufacturer that submitted the designation application.

Review template section	Description of information recorded
Background information: Proposed orphan disease	A description of the drug, the disease, and how the drug is to be used in the disease (i.e., prevention, treatment, or diagnosis).
Background information: Resident agent or contact (if applicable)	Name, address, and contact information for U.S. resident agent, if a foreign manufacturer submitted the designation application.
Background information: Other manufacturer	If the source of the drug is not the manufacturer that submitted the designation application, the information for the other manufacturing source.
Background information: Regulatory status	The U.S. and foreign marketing history of the drug, active investigational new drug applications for the drug, and any adverse actions taken against the drug.
Background information: Manufacturer provided self-certification	Check box indicating yes or no as to whether the manufacturer provided a self-certification stating that it has not submitted an application to market the drug to treat this disease.
Background information: Orphan drug designation history	All orphan designation applications or designations granted for the drug for this disease in the United States and in Europe, and all orphan designations for any drug to treat this disease.
Background information: Disease proposed by manufacturer	Description of the disease the drug is intended to treat.
Clinical superiority analysis: "Same drug" is already approved for the same disease	Check box to indicate yes or no as to whether the same drug is already approved for the same disease. If yes, a list of the same drug(s) already approved for this disease.
Clinical superiority analysis: Adequate claim of clinical superiority (if applicable)	Check box to indicate yes or no as to whether the manufacturer provided an adequate explanation of why the same drug and disease combination may be clinically superior to the already approved drug. Regardless of response, a description of clinical superiority claims made in the designation application.
Clinical superiority analysis: Analysis of clinical superiority claim (if applicable)	If the reviewer agrees with the manufacturer's clinical superiority claim, a description of the claim that will serve as the basis for orphan designation. If the reviewer does not agree with the manufacturer's clinical superiority claim, an analysis explaining why the claim presented in the designation application is inadequate.
Clinical superiority analysis: Type of clinical superiority (if applicable)	Check box to identify the type of clinical superiority (i.e., safety, efficacy, or major contribution to patient care) that serves as the basis for granting orphan designation, as well as a one-sentence description of the accepted clinical superiority claim.
Orphan subset analysis: Orphan subset of a non-rare disease	Check box to indicate yes or no as to whether orphan designation is requested for an orphan subset of a non-rare disease.
Orphan subset analysis: Designation for a pediatric subpopulation of a non-rare disease	Check box to indicate yes or no as to whether the manufacturer is requesting orphan designation for a pediatric subpopulation of a non-rare disease.
Orphan subset analysis: Property of drug that limits its use to subset of a non-rare disease (if applicable)	Check box to indicate yes or no as to whether the manufacturer submitted evidence supporting that a property of the drug would limit its use to a subset of a non-rare disease.
Orphan subset analysis: Orphan subset claim description (if applicable)	If the reviewer agrees with the orphan subset claim, a description of the drug's property that limits its use to the orphan subset. If the reviewer does not agree with the orphan subset claim, a description of the claim provided in the designation application.
Population estimate: Population estimate for disease and methodology used	Description of the manufacturer's population estimate of the disease, methodology for estimating it, and sources provided for supporting it. Additionally, a description of the reviewer's evaluation of the manufacturer's population estimate, including the results of independent verification.

Review template section	Description of information recorded
Population estimate: Reviewer agrees that the population estimate is less than 200,000	Check box to indicate yes or no as to whether the OOPD reviewer agrees that the disease the drug is intended to treat affects fewer than 200,000 people in the United States.
Population estimate: Reviewer concerns with the population estimate (if applicable)	Description of any concerns about the manufacturer's population estimate, including any calculations performed by the OOPD reviewer to determine the estimated population of the disease.
Scientific rationale: Scientific rationale	Description of the drug and the rationale for expecting it to effectively treat the rare disease based on human data, animal data, or in vitro data.
Scientific rationale: Disease treated by drug is the disease that is the subject of the designation application	Check box to indicate yes or no as to whether the disease treated by the drug is the same disease for which the manufacturer has applied for orphan designation. If applicable, a description of the disease that the reviewer determined the drug would treat and an explanation of why it varied from the disease identified in the designation application.
Scientific rationale: Designation application relies on human data	Check box to indicate yes or no as to whether the manufacturer provided data from human studies to support its scientific rationale. If applicable, a brief description of the best human data used to support the scientific rationale, noting any other human data also provided.
Scientific rationale: Designation application relies on animal model data	Check box to indicate yes or no as to whether the manufacturer provided data from an animal model of the disease to support its scientific rationale. If applicable, a brief description of the animal data provided to support the scientific rationale and the reviewer's assessment of the adequacy of this data (e.g., whether it is an appropriate animal model).
Scientific rationale: Appropriate animal model of the disease if no animal or human data provided	Check box to indicate yes or no as to whether there is an appropriate animal model of the disease available, but not provided by the manufacturer.
Scientific rationale: In vitro data and other data to support an adequate scientific rationale (if applicable)	Check box to indicate yes or no as to whether the manufacturer provided in vitro data or other data to support its scientific rationale. If applicable, a description of the in vitro or other data that was used to support an adequate scientific rationale.
Reviewer's evaluation and recommendation: Recommendation	Check box to indicate OOPD reviewer's recommendation for orphan status (i.e., designate, pending, or denial).
Reviewer's evaluation and recommendation: Summary of recommendation	Summary of the reviewer's evaluation of the designation application, which may outline specific concerns about the designation application to include in OOPD's decision letter for the manufacturer.
Reviewer's evaluation and recommendation: Secondary reviewer comments	Comments from the secondary reviewer, such as whether a meeting with the manufacturer is recommended to discuss the designation application.

Source: GAO analysis of Food and Drug Administration (FDA) documents. | GAO-19-83

Appendix II: Orphan Drug Marketing Approvals from 2008 to 2017

The Food and Drug Administration (FDA) approved 351 orphan drugs for marketing from 2008 to 2017 in 27 different therapeutic areas.[1] Forty-two percent (149) of orphan drug marketing approvals were in oncology, with six other therapeutic areas having 10 or more approved orphan drugs. (See table 7 for information on orphan drug marketing approvals from 2008 to 2017 by therapeutic area.) Additionally, the 351 orphan drug marketing approvals were for 252 unique drugs, because drugs can be approved for more than one orphan indication. The majority of drugs had one orphan indication (77.4 percent) or two orphan indications (15.9 percent). However, several drugs (6.7 percent) were approved to treat three or more orphan indications.

Table 7: Orphan Drug Marketing Approvals from 2008 to 2017 in Each Therapeutic Area

Therapeutic area	Unique orphan drugs approved for marketing in therapeutic area (number of indications per drug if more than one)[a]	Number of approved marketing indications per therapeutic area
Oncology	Abraxane, Adcetris (5), Afinitor (4), Alecensa (2), Aliqopa, Alunbrig, Arzerra (4), Avastin (9), Bavencio, Beleodaq, Bendeka (2), Besponsa, Blincyto, Bosulif (2), Calquence, Caprelsa, Cometriq, Cotellic, Cyramza (2), Darzalex (3), Defitelio, Empliciti, Erwinase, Farydak, Folotyn, Fusilev (2), Gazyva (3), Gilotrif (2), Gleevec (2), Halaven, Herceptin, Iclusig (2), Idhifa, Imbruvica (9), Imlygic, Iressa, Istodax (2), Keytruda (4), Kymriah (Tisagenlecleucel), Kyprolis, Lartruvo, Lenvima, Lynparza (2), Marqibo, Mekinist (3), Mylotarg, Nexavar, Ninlaro, Oforta, Onivyde, Opdivo (6), PEG-Intron, Pomalyst, Portrazza, Purixan, Revlimid (3), Rituxan, Rituxan Hycela (3), Rubraca, Rydapt (2), Sprycel, Steritalc, Stivarga (2), Synribo, Tafinlar (2), Tagrisso, Treanda (2), Unituxin, Valchlor, Velcade (2), Venclexta, Voraxaze, Votrient, Vyxeos, Xalkori (2), Xatmep, Yervoy (3), Yescarta (3), Yondelis, Zejula, Zelboraf, Zydelig (2), Zykadia (2)	149

[1]FDA officials told us that the therapeutic areas identified in the orphan drug data they provided were for the purposes of this analysis and may not always reflect the review division responsible for the marketing approval.

Therapeutic area	Unique orphan drugs approved for marketing in therapeutic area (number of indications per drug if more than one)[a]	Number of approved marketing indications per therapeutic area
Hematology	Alprolix, Atryn, Coagadex, Corifact (2), Eloctate, Endari, Evomela, Exjade - Jadenu Sprinkles (3), Feiba, Ferriprox, Gammaplex, Hemlibra, Idelvion, Jakafi (2), Kcentra (2), Mozobil, Novoseven, Nplate, Obizur, Praxbind, Promacta (2), Provayblue, Riastap, Rixubis, Siklos, Soliris, Sylvant, Tepadina, Tretten, Vonvendi, Wilate, Zelboraf	38
Metabolic	Ascor, Carbaglu, Cerdelga, Cholbam, Crestor, Elelyso, Juxtapid, Kanuma, Kynamro, Lumizyme (2), Mepsevii, Myalept, Ocaliva, Orfadin, Procysbi (3), Ravicti (2), Repatha, Strensiq, Vimizim, Vpriv, Xiruden	25
Neurology	Abilify, Ampyra, Austedo, Banzel, Brineura, Carnexiv, Cuvposa, Duopa, Dysport, Emflaza, Exondys 51, Gammagard, Gamunex-C, Gocovri, H.P. Acthar Gel, Hetlioz, Keveyis, Nymalize, Onfi, Radicava, Sabril, Soliris, Spinraza, Xenazine	24
Rheumatology	Actemra, Arcalyst, Colcrys, Humira (2), Ilaris (5), Kineret, Krystexxa, Xatmep	13
Immunology	Actemra, Berinert, Cinryze, Firazyr, Haegarda, Imbruvica, Kalbitor (2), Prevymis, Rituxan, Ruconest	11
Ophthalmology	Cystaran, Durezol, Humira, Luxturna, Membraneblue, Mitosol, Ozurdex, Photrexa Viscous (2), Zirgan	10
Anti-infective	BAT, Benznidazole,[b] Cayston, Coartem, Cresemba (2), Impavido, Sirturo, Vermox	9
Cardiovascular	Adcirca, Adempas (2), Northera, Opsumit, So-Aqueous, Tracleer, Tyvaso, Uptravi	9
Endocrine	Korlym, Macrilen, Natpara, Signifor LAR (2), Somatuline Depot (2), Triptodur, Zemplar	9
Pulmonary	Esbriet, Kalydeco, Nucala, Ofev, Orkambi (2), Rapamune, Steritalc	8
Medical imaging	Adreview (2), Gleolan, Lipiodol, Lymphoseek, Netspot, Technetium Tc99m Sulfur Colloid	7
Antiviral	Harvoni, Ixiaro, Norvir, Sovaldi, Varizig, Viread	6
Medical countermeasures	Abthrax, Anthim, Anthracil, Biothrax, Neulasta, Neupogen	6
Antidote	Anascorp, Anavip, Cetylev, Nithiodote, Vistogard	5
Gastroenterology	Gattex, Humira, Remicade, Xermelo, Xifaxan	5
Bone	Sensipar (2), Xgeva (2)	4
Analgesia	Gralise, Horizant, Qutenza	3
Transplant	Envarsus Xr, Nulojix	2
Anesthesia	Ryanodex	1
Dermatology	Humira	1
Diagnostic	Spherusol	1
Orthopedics	Xiaflex	1
Other[c]	Hemangeol	1
Renal	Phoxilium	1
Reproductive	Makena	1

Therapeutic area	Unique orphan drugs approved for marketing in therapeutic area (number of indications per drug if more than one)[a]	Number of approved marketing indications per therapeutic area
Urology	Xiaflex	1

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-19-83

Note: FDA officials told us that the therapeutic areas identified in the orphan drug data they provided were for the purposes of this analysis and may not always reflect the review division responsible for the marketing approval.

[a]An approved orphan drug may appear in more than one therapeutic area. For example, Humira has approved marketing indications in dermatology, gastroenterology, ophthalmology, and rheumatology.

[b]Benznidazole is the generic name as FDA data did not list a trade name for this drug.

[c]FDA labeled one therapeutic area as “other,” which had one orphan drug marketing approval. The approval was for Hemangeol, a drug that treats proliferating infantile hemangiomas (birthmarks that most commonly appear as rubbery, bright red nodules of extra blood vessels in the skin) requiring systemic therapy.

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

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

NOV 15 2018

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

Dear Mr. Dicken:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "*ORPHAN DRUGS: FDA Should Ensure Designation Review Consistency; Rare Disease Drug Development Challenges Continue*" (GAO-19-83).

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

Sincerely,

Matthew D. Bassett
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED – ORPHAN DRUGS: FDA SHOULD ENSURE DESIGNATION REVIEW CONSISTENCY, RARE DISEASE DRUG DEVELOPMENT CHALLENGES CONTINUE (GAO-19-83)

HHS appreciates GAO's recognition of FDA's recent achievements in the orphan-drug designation program and in the rare disease drug development space. GAO noted that FDA applies consistent criteria in reviewing requests for orphan-drug designation and highlighted the many achievements of the Orphan Drug Modernization Plan, including FDA's successful clearance of the orphan-drug designation request backlog nearly a month ahead of the established goal. GAO recognized that FDA has consistently met its 90-day timeliness goal since mid-September 2017. Finally, GAO credited FDA with developing guidance and training to better inform FDA reviewers and the public about addressing the challenges in rare disease drug development.

Recommendation 1

The Commissioner of FDA should ensure that information from orphan drug designation applications is consistently recorded in OOPD review templates and evaluated by OOPD reviewers when making an orphan designation decision.

HHS Response

HHS concurs with GAO's recommendation to consistently record and evaluate information in the FDA Office of Orphan Products Development (OOPD) review templates during orphan-drug designation review and the feedback provided by GAO in this report will be considered in FDA's ongoing efforts to evaluate and revise the pilot review template and train reviewers.

FDA is committed to meeting goals of the Orphan Drug Modernization Plan to provide accurate, efficient, and timely reviews of requests for orphan-drug designation. FDA implemented the pilot review template under the modernization plan in October 2017 to increase consistency, efficiency, and predictability of orphan-drug designation reviews. The 148 orphan-drug designation reviews (from October to December 2017) that GAO examined were some of the first reviews that OOPD completed using the new pilot template.

Of the five sections in the pilot review template, GAO noted that OOPD reviewers did not consistently record or utilize information in the background section, including the regulatory history of the drug and the disease. Information recorded in this section may provide useful context for the reviewer regarding FDA's historical experience in evaluating the drug or the disease, however, will not typically affect the outcome of the orphan-drug designation decision. Because orphan-drug designation occurs early in drug development, many drugs that are the subject of an orphan-drug designation request do not have relevant regulatory history background to document. GAO noted that some reviews lacked documentation of "adverse actions" taken against the drug, however, it would be extremely rare for a drug at the designation stage to have had any adverse actions taken against it. Nevertheless, FDA recognizes the importance of consistently documenting and utilizing information and will continue to apply consistent criteria for its review decisions.

Page 1 of 1

Appendix IV: 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, Marcia Crosse (Director), Robert Copeland (Assistant Director), E. Jane Whipple (Analyst-in-Charge), and Brienne Tierney made key contributions to this report. Also contributing were Kaitlin Farquharson, Alison Granger, Drew Long, and Vikki Porter.

Appendix V: Accessible Data

Data Tables

Accessible Data for Orphan Designation Applications Received and Designations Granted from 2008 to 2017, as of April 2018

n/a	Year									
Category	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
Orphan designation applications received	185	250	323	307	267	339	453	471	568	527
Orphan designations granted	135	178	207	212	195	254	357	353	401	323

Accessible Data for Figure 3: Orphan Designation Applications Received and Designations Granted from 2008 to 2017, as of April 2018

n/a	Year									
Category	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
Orphan designation applications received	185	250	323	307	267	339	453	471	568	527
Orphan designations granted	135	178	207	212	195	254	357	353	401	323

Accessible Data for Figure 4: Number of Orphan Designation Applications from 2008 to 2017, by Population Estimate

Category	Population estimates	Number of applications
Represent 71 percent of orphan designation application	0-50,000	1,324
	50,001-100,000	550
n/a	100,001-150,000	367
n/a	150,001-200,000	404

Accessible Data for Figure 5: Therapeutic Areas of Orphan Designation Applications FDA Received from 2008 to 2017

Category	Percentage
Oncology	30
Neurology	13
Hematology	7
Gastroenterology/Liver	6
Infectious Diseases	5
Pulmonary	5
Other (35 areas)	34

Accessible Data for Figure 6: Number of Orphan Drug Marketing Approvals by New Drug or New Indication, 2008 to 2017

n/a	Year									
Category	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
New druga	12	17	8	18	19	18	26	35	17	46
New indication for a previously approved drug	5	3	7	8	7	15	23	13	23	31

Accessible Data for Figure 7: Percent of Orphan Drugs Benefitting from Each Type of FDA Expedited Program in Year Approved, 2008 to 2017

n/a	Year									
Category	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
Breakthrough therapy designation	0	0	0	0	0	6.06	20.41	25	22.5	31.17
Accelerated approval	17.65	20	6.67	26.92	26.92	9.09	22.45	12.5	17.5	20.78
Fast track designation	29.41	35	26.67	46.15	42.31	33.33	32.65	27.08	22.5	22.08
Priority review	70.59	50	73.33	73.08	50	42.42	73.47	62.5	70	66.23

Agency Comment Letter

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

Page 1

NOV 15 2018

John E. Dicken Director, Health Care

U.S. Government Accountability Office

441 G Street NW

Washington, DC 20548

Dear Mr. Dicken:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "ORPHAN DRUGS: FDA Should Ensure Designation Review Consistency; Rare Disease Drug Development Challenges Continue" (GAO-19-83).

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

Sincerely,

Matthew D. Bassett

Assistant Secretary for Legislation

Attachment

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HHS appreciates GAO's recognition of FDA' s recent achievements in the orphan-drug designation program and in the rare disease drug development space. GAO noted that FDA applies consistent criteria in reviewing requests for orphan-drug designation and highlighted the many

achievements of the Orphan Drug Modernization Plan, including FDA's successful clearance of the orphan-drug designation request backlog nearly a month ahead of the established goal. GAO recognized that FDA has consistently met its 90-day timeliness goal since mid-September 2017. Finally, GAO credited FDA with developing guidance and training to better inform FDA reviewers and the public about addressing the challenges in rare disease drug development.

Recommendation 1

The Commissioner of FDA should ensure that information from orphan drug designation applications is consistently recorded in OOPD review templates and evaluated by OOPD reviewers when making an orphan designation decision.

HHS Response

HHS concurs with GAO's recommendation to consistently record and evaluate information in the FDA Office of Orphan Products Development (OOPD) review templates during orphan-drug designation review and the feedback provided by GAO in this report will be considered in FDA's ongoing efforts to evaluate and revise the pilot review template and train reviewers.

FDA is committed to meeting goals of the Orphan Drug Modernization Plan to provide accurate, efficient, and timely reviews of requests for orphan-drug designation. FDA implemented the pilot review template under the modernization plan in October 2017 to increase consistency, efficiency, and predictability of orphan-drug designation reviews. The 148 orphan-drug designation reviews (from October to December 2017) that GAO examined were some of the first reviews that OOPD completed using the new pilot template.

Of the five sections in the pilot review template, GAO noted that OOPD reviewers did not consistently record or utilize information in the background section, including the regulatory history of the drug and the disease. Information recorded in this section may provide useful context for the reviewer regarding FDA's historical experience in evaluating the drug or the disease, however, will not typically affect the outcome of the orphan-drug designation decision. Because orphan-drug designation occurs early in drug development, many drugs that are the subject of an orphan-drug designation request do not have relevant regulatory history background to document. GAO noted that some reviews lacked

documentation of "adverse actions" taken against the drug, however, it would be extremely rare for a drug at the designation stage to have had any adverse actions taken against it. Nevertheless, FDA recognizes the importance of consistently documenting and utilizing information and will continue to apply consistent criteria for its review decisions.

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