



September 2019

INVESTIGATIONAL DRUGS

FDA and Drug Manufacturers Have Ongoing Efforts to Facilitate Access for Some Patients

Accessible Version

Why GAO Did This Study

When investigational drugs show promise for treating serious or life-threatening diseases, patients are often interested in obtaining access to them. Congress included a provision in the FDA Reauthorization Act of 2017 for GAO to review actions taken to facilitate access to these drugs.

This report describes (1) actions FDA and drug manufacturers have taken to broaden eligibility criteria for clinical trials, (2) actions FDA has taken to facilitate access to investigational drugs outside of clinical trials, and (3) information drug manufacturers have communicated to patients and physicians about access to investigational drugs outside of clinical trials.

GAO reviewed laws, regulations, FDA documents, and manufacturer policies and interviewed FDA officials and a non-generalizable selection of 10 manufacturers and 14 other stakeholders (including patient advocacy and physician organizations). The manufacturers were developing drugs to treat serious or life-threatening diseases, and were selected for variation in company size. GAO also reviewed information that a non-generalizable selection of 29 manufacturers communicated through their websites about access to investigational drugs outside of clinical trials. GAO selected manufacturers for variation in the type of serious diseases their investigational drugs were intended to treat, company size, and other factors.

HHS provided technical comments on a draft of this report, which GAO incorporated as appropriate.

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FDA and Drug Manufacturers Have Ongoing Efforts to Facilitate Access for Some Patients

What GAO Found

Individuals may access investigational drugs—those not yet approved for marketing in the United States by the Food and Drug Administration (FDA)—by participating in clinical trials conducted by drug manufacturers to test drug effectiveness and safety. FDA has ongoing efforts to help manufacturers identify the circumstances under which they could broaden clinical trial eligibility criteria to include patients who are commonly excluded, such as pediatric patients and patients with impaired liver and kidney function, without compromising study results.

- FDA issued guidance in March 2019 with recommendations on ways manufacturers could broaden eligibility criteria for cancer clinical trials, when clinically appropriate. In June 2019, FDA issued related guidance that applies to a wider range of clinical trials beyond cancer trials.
- One of the 10 manufacturers GAO interviewed reported broadening its eligibility criteria to include more patients, such as those with HIV. Another manufacturer has begun reviewing its eligibility criteria and expects to include adolescents, as appropriate, in future studies—a population that has generally been excluded from trials. However, these and two other manufacturers cited challenges in these efforts. One stated that expanding participation to patients who use other medications, for example, could adversely affect a study's ability to identify the effects of the studied drug.

Outside of clinical trials, patients with certain medical conditions, who are unable to enroll in a clinical trial, and have no other comparable medical options, may request to obtain access to investigational drugs. This can occur under FDA's expanded access program, or through a 2018 federal law known as "Right to Try." Under either pathway, a patient can only access the investigational drug if its manufacturer agrees to the request. FDA has taken steps to facilitate access to investigational drugs outside of clinical trials, and most manufacturers in GAO's review communicated information to patients and physicians through their websites about how to access their investigational drugs outside of clinical trials. For example:

- Since 2017, FDA took steps to simplify its expanded access program to make it easier to participate. In addition, to address concerns raised by manufacturers, FDA clarified guidance on how it would review data resulting from the program. Seven of the 10 manufacturers GAO interviewed viewed the guidance as an improvement.
- GAO's review of information communicated by 29 manufacturers on their websites found that 23 had policies about accessing investigational drugs outside of clinical trials. At the time of GAO's review, 19 of the 23 stated they would consider individual requests for access, while the other four stated they would not. More than half of the manufacturers stated that if they approve a request, they require additional steps, such as FDA review of the request.

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Abbreviations

Federal RTT Act	federal Right to Try Act
FDA	Food and Drug Administration
FDARA	Food and Drug Administration Reauthorization Act of 2017
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IND	investigational new drug application
IRB	institutional review board

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September 9, 2019

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

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

Before drugs or biologics are approved for marketing in the United States by the Food and Drug Administration (FDA), they are considered investigational.¹ As part of the drug development process, these investigational drugs are tested for safety and effectiveness on humans in clinical trials. When investigational drugs show promise for treating serious or life-threatening diseases or conditions such as metastatic cancer, patients and physicians are often interested in obtaining access to them before they are approved.² While some patients may obtain access to these drugs by participating in clinical trials, not all patients are able to participate—for example, because they do not meet the eligibility

¹See 21 C.F.R. § 312.3 (2018). Drugs are defined to include, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and include components of those articles. See 21 U.S.C. §§ 321(g)(1)(B),(D). Biologic products (referred to as biologics in this report) are materials, such as viruses, therapeutic sera, toxins, antitoxins, vaccines, or analogous products to prevent, treat, or cure human diseases or injuries. See 21 C.F.R. § 600.3(h) (2018). In general, biologics are derived from living sources, such as humans, animals, and microorganisms. For the purpose of this report, we refer to drugs and biologics collectively as “drugs.”

²A disease is characterized by specific signs and symptoms (e.g., Alzheimer’s disease) whereas a condition is an unhealthy state (e.g., chronic pain).

criteria that manufacturers have established for enrolling in a study.³ Questions have been raised in recent years about whether clinical trial eligibility criteria are too narrow and exclude patients who are likely to be treated once a drug is approved, and FDA has historically provided guidance to manufacturers to help them consider the circumstances under which they could broaden these criteria without compromising study results or raising ethical issues.⁴

Outside of clinical trials, patients who are unable to participate in the trials, and who have certain medical conditions, such as life-threatening conditions, and no comparable medical options, can seek access to investigational drugs through two pathways: 1) FDA's expanded access program and 2) the federal Right to Try Act (federal RTT Act).⁵ Under either of these two pathways, access to the investigational drug can only occur if the drug manufacturer agrees to provide access.

Requests to obtain access to investigational drugs through FDA's expanded access program must be reviewed by both FDA and an institutional review board (IRB) in addition to being agreed upon by the drug manufacturer.⁶ Some stakeholders—including physician and patient advocacy groups—have criticized FDA's program for being too complex

³Eligibility criteria define the patient population to be studied in a clinical trial. Inclusion criteria specify the characteristics required for participation, such as the stage of a disease. Exclusion criteria specify the characteristics that disqualify patients from participation, such as the presence of comorbidities or being too young or too old.

⁴For example, FDA has issued guidance documents with recommendations to include patient populations in clinical trials that have been typically excluded from participation, such as elderly patients and pregnant women. See Food and Drug Administration, *Guideline for the Study of Drugs Likely to be Used in the Elderly* (Rockville, Md.: November 1989) and *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Draft Guidance for Industry* (Silver Spring, Md.: April 2018).

⁵See Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 402, 111 Stat. 2296, 2365 (authorizing expanded access) (codified as amended at 21 U.S.C. § 360bbb); Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, Pub. L. No. 115-176, 132 Stat. 1372 (2018) (codified at 21 U.S.C. § 360bbb-0a).

⁶FDA determines whether to allow expanded access requests to proceed, after which an IRB must approve patients' expanded access treatment plans.

An IRB is any board, committee, or other group formally designated by an institution to review, approve the initiation of, and conduct periodic review of biomedical research involving human subjects. The primary responsibility of an IRB is to ensure protections for human volunteers in clinical trials and that informed consent will be obtained.

and burdensome to entities involved, which they contend could pose a barrier to individual patients' access to these drugs. However, others argue that FDA is not a barrier because it allows most requests for expanded access to proceed and because factors beyond FDA's program—such as a manufacturer's approval—prevent patients from obtaining access. In 2017, we found that FDA allowed 99 percent of the requests under its expanded access program to proceed. We also found that the agency and other stakeholders had taken steps to simplify and improve the expanded access process.⁷ For example, FDA shortened the form required for individual patient requests, and it partnered with the Reagan-Udall Foundation to develop a website—referred to as the Expanded Access Navigator—to help physicians and patients locate drug manufacturers' expanded access policies.⁸

The other pathway for obtaining investigational drugs outside of clinical trials—the federal RTT Act—was established by law in May 2018. This provided another pathway for individuals with life-threatening diseases or conditions to seek access to investigational drugs without a requirement for FDA or IRB involvement.⁹ Some stakeholders, including some

⁷GAO, *Investigational New Drugs: FDA Has Taken Steps to Improve the Expanded Access Program but Should Further Clarify How Adverse Events Data Are Used*, [GAO-17-564](#) (Washington, D.C.: July 11, 2017).

⁸The Reagan-Udall Foundation is a non-profit organization that was established by Congress to assist FDA. See 21 U.S.C. § 379dd. The Expanded Access Navigator was launched in July 2017. See Reagan-Udall Foundation, *Expanded Access Navigator*, accessed May 28, 2019, <http://navigator.reaganudall.org/>. This website complemented a provision in the 21st Century Cures Act that required certain manufacturers to make their expanded access policies publicly available. Pub. L. No. 114-255, § 3032, 130 Stat. 1033, 1100 (2016) (codified as amended at 21 U.S.C. § 360bbb-0). Under this requirement, as amended by the FDA Reauthorization Act of 2017, manufacturers must make their policies publicly available, such as by posting them on a publicly available internet website, beginning on the earlier of (a) the initiation of a phase II or phase III study for a drug or (b) as applicable, 15 days after the drug receives a designation as a breakthrough therapy, fast track product, or regenerative advanced therapy. 21 U.S.C. § 360bbb-0(f) (as amended by Pub. L. No. 115-52, § 610(c), 131 Stat. 1005, 1053).

⁹A number of states have enacted related legislation, referred to as Right-to-Try laws, placing limitations under state law on liability and licensing actions against individuals or entities involved in the care of individuals seeking access to drugs that have successfully completed phase I clinical trials and met other conditions. By May 2018, 40 states had enacted such laws. See National Conference of State Legislatures, *“Right to Try” Experimental Prescription Medicines State Laws and Legislation for 2014–2018*, accessed June 13, 2019, http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx#Right_to_Try.

physicians and medical ethicists, have questioned whether patient safety could be compromised by allowing access to investigational drugs without FDA and IRB review and whether the new pathway will improve access for patients because it does not compel manufacturers to allow access to their investigational drugs.

The FDA Reauthorization Act of 2017 (FDARA) included a provision for us to describe actions taken by FDA and drug manufacturers to facilitate individual access to investigational drugs.¹⁰ This report examines

1. actions FDA and drug manufacturers have taken to broaden patient eligibility criteria for clinical trials,
2. actions FDA has taken to help facilitate access to investigational drugs outside of clinical trials, and
3. information drug manufacturers have communicated to patients and physicians about access to their investigational drugs outside of clinical trials.

To describe what actions FDA and drug manufacturers have taken to broaden patient eligibility criteria for clinical trials, we reviewed FDA guidance, reports and other related documents and interviewed knowledgeable FDA officials about the agency's ongoing or planned actions on this topic. We also analyzed information collected through interviews with, or written responses to, questions from a non-generalizable selection of 10 drug manufacturers about any ongoing or planned actions they had to broaden the eligibility criteria for their clinical trials, challenges associated with broader criteria, and other efforts to increase participation in clinical trials. We selected the drug manufacturers to achieve variation in company size and because they were developing drugs or biologics to treat serious or life-threatening diseases or conditions.

To describe what actions FDA has taken to help facilitate access to investigational drugs outside of clinical trials, we reviewed laws, FDA regulations and guidance, and FDA's website and other related documents about FDA's expanded access program and the federal RTT pathway. We also interviewed knowledgeable FDA officials about the agency's ongoing and planned actions related to this topic and a non-

¹⁰Pub. L. No. 115-52, § 610(a)(2), 131 Stat. 1052.

generalizable selection of 24 stakeholder organizations to obtain their views on FDA's actions. The organizations included the 10 selected manufacturers noted above; three trade groups representing manufacturers; three patient advocacy organizations; two physician organizations; two public policy research organizations; two organizations that work with manufacturers to facilitate access outside of clinical trials; one organization focused on improving access to investigational drugs through clinical trials; and one physician representing a research organization. We selected patient advocacy and physician organizations that broadly represented the views of patients and physicians, including those stating they have experience in seeking access to investigational drugs outside of clinical trials. In addition, we selected organizations to provide a range of perspectives regarding FDA's expanded access program and the federal RTT pathway.

To describe what information drug manufacturers have communicated to patients and physicians about access to their investigational drugs outside of clinical trials, we reviewed the websites of a non-generalizable selection of 29 drug manufacturers.¹¹ We first selected 21 drug manufacturers that were developing investigational drugs or biologics intended to treat 10 serious diseases to achieve variation across several factors.¹² These factors included company size, participation in the Expanded Access Navigator, and whether the manufacturer had an investigational drug or biologic that FDA designated as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy in fiscal year 2018.¹³ Two of these 21 manufacturers were among the 10 we interviewed. In addition, we reviewed the websites of the other eight drug manufacturers we interviewed. We conducted our review of manufacturer

¹¹Manufacturers are required to make such information "public and readily available, such as by posting such policies on a publicly available Internet website." 21 U.S.C. § 360bbb-0(b).

¹²We selected the following 10 serious diseases: Duchenne muscular dystrophy, Alzheimer's disease, pancreatic cancer, metastatic breast cancer, acute myeloid leukemia, human immunodeficiency virus (HIV) infection, schizophrenia, cystic fibrosis, hemophilia type a or b, and chronic heart failure. We selected these 10 diseases because they are generally recognized as serious and reflect a range of types of diseases (e.g., neurological, viral, psychiatric, cancer).

¹³Manufacturers voluntarily participate in the Expanded Access Navigator by providing links to their expanded access policies posted on their websites. Breakthrough therapy, fast track product, and regenerative medicine advanced therapy designations are used by FDA to expedite the development and review of certain drugs and biologics intended to treat conditions that are generally considered serious.

websites between January 31, 2019, and March 12, 2019, by using a data collection instrument that included a standard set of questions for collecting information on the availability of information, procedures for making a request for access to investigational drugs, and the factors that the manufacturer would consider in evaluating requests. For manufacturers that we determined had not communicated information on their websites about access to investigational drugs at the time of our review, we contacted them to verify this. To supplement our analysis, we reviewed additional information that manufacturers communicated on their websites, such as whether they provided information about access to specific investigational drugs.

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

Background

Clinical Trials

When patients are seeking access to investigational drugs, their first option is to consider whether they can obtain them through participation in a clinical trial. Clinical trials are a step in the drug development process through which a drug manufacturer assesses the safety and effectiveness of its investigational drug through human testing. A clinical trial can take place in a variety of settings (e.g., research hospitals, universities, and community clinics) and geographic locations, and is led by a principal investigator that is typically a physician.

Manufacturers establish clinical trial eligibility criteria to define the patient population to be studied, and only patients who meet those criteria can participate. These criteria can vary depending on the drug being studied and its intended use. Patient eligibility criteria consist of both inclusion and exclusion criteria. Inclusion criteria specify the characteristics of the patient that are required for participation, such as the stage or characteristics of a disease, and typically identify a patient population in which it is expected that the manufacturer can demonstrate the effect of an investigational drug. In comparison, exclusion criteria specify the

characteristics that disqualify patients from clinical trial participation and can include factors that could mask the effect of an investigational drug, such as the presence of comorbidities or simultaneous use of other drugs.¹⁴ Certain patient populations, such as children and pregnant women, may also be excluded from clinical trial participation because of ethical reasons.¹⁵

Drug manufacturers, FDA, and IRBs each have responsibilities as part of the clinical trial process. In order to test an investigational drug on human volunteers in clinical trials, a manufacturer must first submit an investigational new drug application (IND) to FDA. FDA is responsible for reviewing the IND, which includes various components such as the clinical trial protocol that describes the patient eligibility criteria, the medications and dosages to be studied, and other details. In turn, an IRB is responsible for reviewing and approving the clinical trial protocol as well as reviewing the informed consent form for the study.¹⁶ In general, clinical trials that involve human volunteers can begin after FDA has reviewed and allowed the IND to proceed and the IRB has given its approval.

An investigational drug typically goes through three phases of clinical trials before an application is submitted to FDA for marketing approval.¹⁷ At any point during the clinical trials, FDA could issue a clinical hold on the existing IND that would delay the proposed clinical trials or suspend the ongoing clinical trials. When a proposed or ongoing study is placed on a complete clinical hold, the investigational drug cannot be administered

¹⁴A comorbidity is a medical condition beyond the condition an investigational drug is intended to treat.

¹⁵For example, pregnant women have been excluded because of concerns about the potential for injury to the fetus.

¹⁶Many institutions (such as research hospitals) have their own IRB to oversee human subjects research conducted within the institution or by the staff of the institution—these are commonly referred to as local IRBs. A physician who does not have access to a local IRB typically uses an independent IRB, which is not associated with any institution.

¹⁷According to FDA officials, in some cases when a new drug is being tested for a life-threatening condition, the drug development process may be expedited by going through only one or two phases of clinical trials before an application is submitted to FDA for marketing approval. In addition, postmarket studies are required for some drugs that FDA has approved for marketing.

to any human volunteers.¹⁸ Traditionally, the three clinical trial phases are the following:

- **Phase I:** This clinical trial phase generally tests the safety of the drug on about 20 to 80 healthy volunteers. The goal of this phase is to determine the drug's most frequent side effects and how it is metabolized and excreted. If the drug does not show unacceptable toxicity in the phase I clinical trials, it may move on to phase II.
- **Phase II:** This clinical trial phase assesses the drug's safety and effectiveness on people who have a certain disease or condition, and typically the assessment is conducted on a few dozen to hundreds of volunteers. Generally, during this phase some volunteers receive the drug and others receive a control, such as a placebo. If there is evidence that the drug is effective in the phase II clinical trials, it may move on to phase III.
- **Phase III:** This clinical trial phase generally involves several hundreds to thousands of volunteers who have a certain disease or condition and gathers more information about the drug's safety and effectiveness, again while being compared to a control.

If phase III clinical trials are successfully completed, the drug may move on to FDA's review and approval process. When seeking FDA's approval to market a drug in the United States, the manufacturer submits an application to FDA that includes the data from the safety and efficacy clinical trials for FDA to review.¹⁹ Safety data include clinical trial results about a drug's toxicity (e.g., the highest tolerable dose) and adverse events that may result from exposure to the drug. Efficacy data include information on whether the drug demonstrated a health benefit over a

¹⁸See 21 C.F.R. § 312.42 (2018). A clinical hold may be either a complete clinical hold or a partial clinical hold. Reasons for imposing complete clinical holds can include human volunteers being subject to unreasonable and significant risks of illness or injury from the drug. According to FDA officials, the agency may also place a drug on a partial clinical hold during which the drug cannot be administered to certain types of patients. See Food and Drug Administration, *Guidance for Industry: Submitting and Reviewing Complete Responses to Clinical Holds* (Rockville, Md.: October 2000).

¹⁹When seeking approval for marketing of a new drug in the United States, the manufacturer submits to FDA a new drug application. See 21 C.F.R. § 314.50 (2018). When seeking approval for marketing of a new biologic in the United States, the manufacturer submits to FDA a biologics license application. See 21 C.F.R. § 601.2 (2018).

placebo. FDA reviews the information in the application to either approve or not approve the drug.

FDA's Expanded Access Program

If a patient seeking access to an investigational drug is not able to participate in the drug's clinical trial (e.g., because of the study's eligibility criteria or geographic location), another pathway to potentially obtain access to the drug outside of a clinical trial is through FDA's expanded access program. Under the program, a licensed physician can submit a request for access to an investigational drug for treatment use on behalf of a patient and may do so during or after phase I, II, or III of clinical trials. To allow access to an investigational drug under the program, FDA must determine that a patient has a serious or immediately life-threatening disease or condition and has no other comparable medical options, among other criteria.²⁰

FDA's goals for the program are to facilitate the availability of investigational drugs when appropriate, ensure patient safety, and preserve the clinical trial development process.²¹ FDA is responsible for determining whether to allow individual requests to proceed to treatment once the manufacturer has agreed to provide access.²² If FDA allows the request to proceed, an IRB must approve the clinical treatment plan that is submitted as part of the individual request and review the informed consent form.²³ The licensed physician treating a patient under expanded access would be required to report to FDA any unexpected serious adverse reactions that occur during treatment for which there is a reasonable possibility that the drug caused the reaction.²⁴

²⁰See 21 C.F.R. § 312.305(a) (2018).

²¹FDA's expanded access program includes options through which requests can be submitted for individual patients or for groups of patients. This report focuses on individual patient requests. For more information about the broader expanded access program, see [GAO-17-564](#).

²²For individual requests, physicians can submit FDA Form 3926 (the Individual Patient Expanded Access Investigational New Drug Application) or FDA Form 1571 (the Investigational New Drug Application).

²³See 21 C.F.R. § 312.305(c)(4) (2018).

²⁴See 21 C.F.R. § 312.32(c) (2018).

The Federal RTT Act

In 2018 the federal RTT Act established another pathway through which patients may potentially obtain access to investigational drugs outside of clinical trials. To be eligible under the law, a patient must have been diagnosed with a life-threatening disease or condition, have exhausted approved treatment options, and be unable to participate in a clinical trial involving the investigational drug.²⁵ Obtaining access to investigational drugs through the federal RTT Act primarily requires the involvement of the manufacturer and treating physician. Similar to FDA's expanded access program, treatment can only proceed if the drug manufacturer allows the patient access to its drug. Under the federal RTT Act, the manufacturer is responsible for providing to FDA an annual summary of any use of its drugs under this pathway that includes information on any known serious adverse events.²⁶ The treating physician is responsible for requesting access to the investigational drug for the patient and for obtaining written informed consent from or on behalf of the patient if the manufacturer agrees to provide access. Eligibility of an investigational drug for patient use through this pathway is based on certain criteria, including that the drug has completed phase I clinical trials, the manufacturer has not discontinued clinical development of the drug, and the drug has not been placed on a clinical hold.²⁷ Unlike FDA's expanded access program, the federal RTT Act does not require the FDA or an IRB to review individual requests for access.

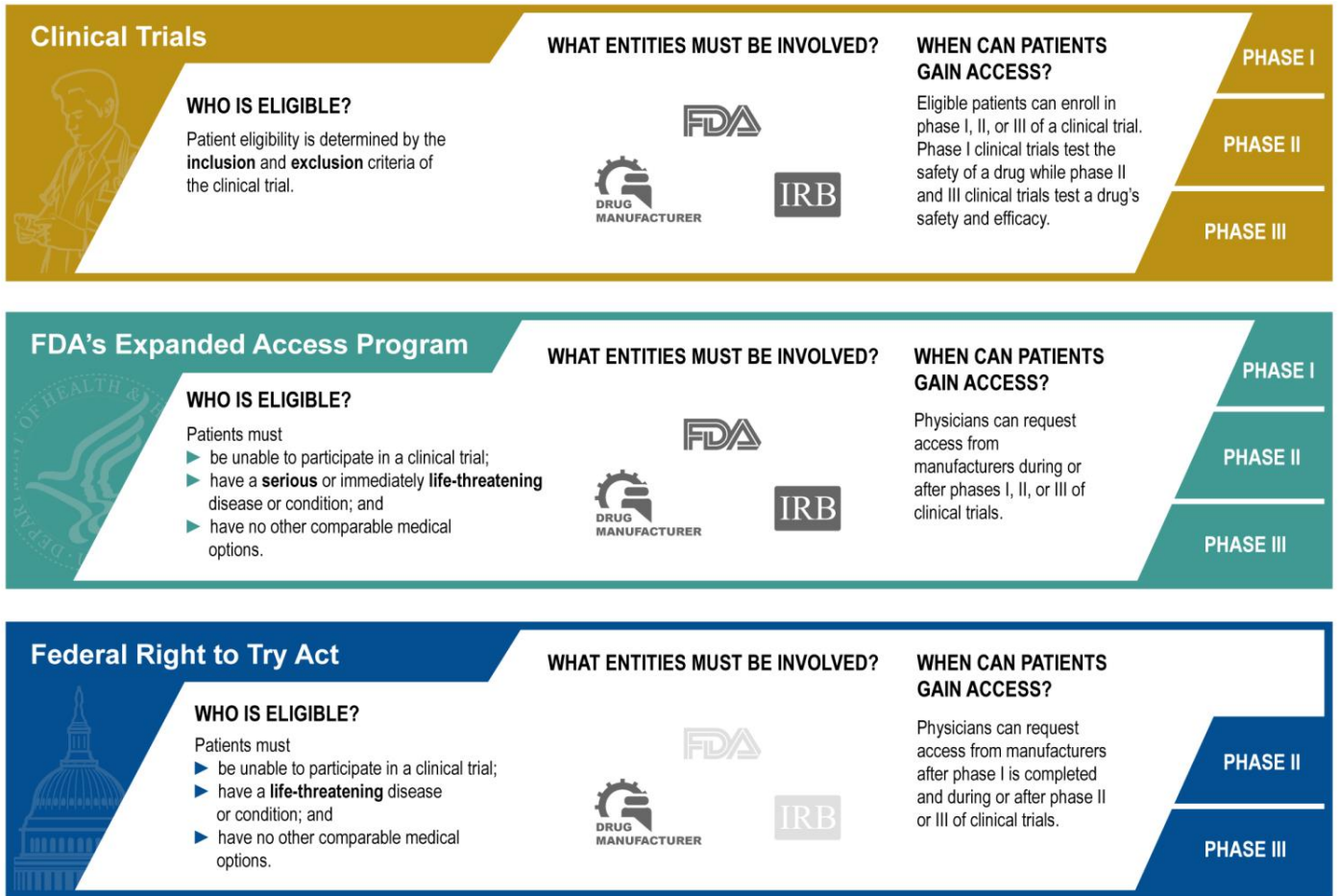
Figure 1 shows a summary of the three pathways through which patients may obtain access to investigational drugs.

²⁵Pub. L. No. 115-176, § 2(a), 132 Stat. 1372 (codified in pertinent part to 21 U.S.C. § 360bbb-0a(a)(1)).

²⁶FDA is also responsible for posting an annual summary report on the use of investigational drugs through the RTT pathway on its website.

²⁷See Pub. L. No. 115-176, § 2(a), 132 Stat. 1372 (codified in pertinent part to 21 U.S.C. § 360bbb-0a(a)(2)).

Figure 1: Access to Investigational Drugs through Three Pathways



FDA = Food and Drug Administration. IRB = institutional review board. Source: GAO analysis of FDA information. | GAO-19-630

FDA Issued Guidance to Help Manufacturers Broaden Clinical Trial Eligibility Criteria and Two Manufacturers We Interviewed Took Steps to Broaden Their Criteria

Some patients, such as those with compromised liver and kidney function, have traditionally been excluded from clinical trials. FDA has ongoing efforts to help drug manufacturers identify the circumstances under which they could broaden their eligibility criteria to include such patients without compromising study results. These efforts include issuing recent guidance with recommendations for including certain patients in clinical trials for cancer drugs. Officials from one of the 10 drug manufacturers we interviewed told us they had broadened their eligibility criteria and another one was taking steps to do so, but these officials and others noted challenges to broadening eligibility criteria.

FDA public workshop on broadening eligibility criteria. In April 2018, FDA held a public workshop with stakeholders—including drug manufacturers, patient advocacy groups, and government agencies—to discuss ways drug manufacturers and other investigators could safely broaden eligibility criteria for clinical trials and to inform FDA guidance on this topic. In July 2018 FDA publicly released a report summarizing the workshop, in accordance with FDARA.²⁸ According to the report, stakeholders at the meeting emphasized the importance of broadening clinical trial eligibility, when appropriate, to include more patients who will likely use the drug if it is approved. Stakeholders recommended that investigators ensure that the eligibility criteria for each of their clinical trials are scientifically justifiable, rather than, for example, “copying and pasting” a narrow set of criteria from a prior study without considering if the exclusions are valid for scientific reasons. According to the report, this practice can unnecessarily limit eligibility for certain patients. While stakeholders commented that assessing whether eligibility criteria are

²⁸FDARA required that FDA, in coordination with other stakeholders, convene a public meeting to discuss clinical trial inclusion and exclusion criteria and make a report on the topics discussed at the meeting available on FDA’s website. See Pub. L. No. 115-52, § 610(a)(1), 131 Stat. 1051 (codified at 21 U.S.C. § 360bbb note).

See Food and Drug Administration, *Public Workshop: Evaluating Inclusion and Exclusion Criteria in Clinical Trials* (Silver Spring, Md.: August 2018).

scientifically justifiable may require additional time and resources, they emphasized it could lead to the removal of unnecessarily restrictive eligibility criteria and thereby increase participation among patient populations that have been typically excluded from clinical trials, such as pediatric patients and patients with compromised liver and kidney function.

FDA guidance on eligibility criteria. In March 2019, FDA issued four new draft guidance documents and finalized one guidance document with recommendations for drug manufacturers to broaden clinical trial eligibility criteria for drugs that treat cancer. The guidance recommends that manufacturers include certain patient populations that have typically been excluded from participation.²⁹ The patient populations are adolescents; pediatrics (children and adolescents); patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infections; patients with brain metastases (i.e., cancer that has spread to the brain); and patients with compromised kidney, heart, or liver function, or who have a history of (or concurrent) cancer. According to FDA, the guidance documents are intended to help drug manufacturers and other investigators broaden cancer trial eligibility criteria. This will help improve patient access to investigational drugs and ensure that the results from the clinical trials are generalizable to patients likely to use the drugs once they are approved. In addition, FDA officials have noted that including broader patient populations in clinical trials can lead to new information in a drug's labeling, which will help communicate the safe and effective use of these drugs. Table 1 provides a summary of each of the five guidance documents.

²⁹See Food and Drug Administration, *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials, Guidance for Industry; Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients, Draft Guidance for Industry; Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections, Draft Guidance for Industry; Cancer Clinical Trial Eligibility Criteria: Brain Metastases, Draft Guidance for Industry; Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies, Draft Guidance for Industry* (Silver Spring, Md.: March 2019). FDA's guidance on the inclusion of adolescent patients in cancer clinical trials is final guidance and its guidance on the inclusion of the other four patient populations is draft guidance. Guidance documents represent FDA's current thinking on a topic. Neither draft nor final guidance documents legally bind FDA or confer legal rights on affected individuals. See 21 C.F.R. § 10.115 (2018). According to FDA, this guidance is intended to assist stakeholders who are responsible for the development and oversight of clinical trials.

Table 1: Summary of the Food and Drug Administration's (FDA) Guidance on Including Certain Patients in Cancer Clinical Trials, March 2019

Patient population	Summary
Pediatric patients	<p>FDA recommends that drug manufacturers consider including pediatric patients in adult cancer trials, in part, to prevent delays in the development of and access to potentially effective new cancer drugs for this population.</p> <p>For example, FDA specifies that children aged 2 to 11 should be considered for inclusion. The guidance recommends that they should be considered for inclusion when there is evidence from adult studies demonstrating that children will likely respond to a drug in a way similar to adults, and when there are no concerns about the potential for toxicity related to severe effects on growth and development.</p>
Adolescent patients	<p>FDA recommends that drug manufacturers consider including adolescents aged 12 to 17 in adult cancer clinical trials, in part, because some cancers found in adolescent patients are similar in biology to those found in adults.</p> <p>For example, the guidance recommends that adolescents should be considered for inclusion in early phase cancer clinical trials if they have cancers that have relapsed and after some initial evidence from adult studies is obtained about a drug's toxicity and effect on the body (e.g., how it is absorbed).</p>
Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infections	<p>FDA recommends that drug manufacturers consider including patients with HIV, HBV, and HCV infections in cancer trials, in part, because HIV and HBV infections can be chronically managed, and HCV infections can be cured with certain anti-viral drugs.</p> <p>For example, the guidance recommends that eligibility criteria for patients with cancer and concurrent HIV infection should focus on patients' immune system functioning and use of drugs to treat HIV. To illustrate, the guidance recommends that patients with a history of certain AIDS-defining infections should be eligible if they have not had the infection within the past 12 months.</p>
Patients with cancer spread to the brain	<p>FDA recommends that drug manufacturers consider including patients with cancers that have spread to the brain in cancer trials, in part, because there is an increasing incidence of patients living with cancers that commonly spread to the brain (e.g., breast and lung cancer).</p> <p>For example, the guidance recommends that patients who have active cancer that has spread to the brain be included in cancer trials, as long as the treating physician has determined that the patient does not require immediate treatment for their central nervous system disease.</p>
Patients with compromised organ function	<p>FDA recommends that drug manufacturers consider including patients with compromised kidney, heart, and liver function in cancer trials, in part, because there is an increasing number of such patients given the increasing life expectancy in the general population.</p> <p>For example, the guidance recommends that as data on a drug's toxicity and other effects on the body (e.g., how it is absorbed) become available during drug development, eligibility criteria should be revised to include patients with compromised organ function where safe parameters regarding dosage adjustments have been determined.</p>

Source: GAO summary of FDA documents. | GAO-19-630

Note: FDA's guidance on the inclusion of adolescent patients in cancer clinical trials is final guidance and its guidance for the other patient populations is draft guidance.

In June 2019, FDA issued draft guidance for manufacturers on broadening clinical trial eligibility criteria, in accordance with FDARA.³⁰ The guidance applies to a wider range of clinical trials beyond cancer trials and includes recommendations to broaden eligibility criteria and considerations for the use of clinical trial designs and other methodologies to help facilitate patient participation.³¹ For example, FDA recommends that manufacturers examine each exclusion criterion to determine if it is needed to help assure the safety of trial participants or to achieve the study's objectives. If not, the manufacturer should consider eliminating or modifying the criterion to expand the study population as well as tailoring the exclusion criteria as narrowly as possible to avoid unnecessary restrictions to the study population.

Two manufacturers' efforts to broaden eligibility criteria. Officials from one of the 10 drug manufacturers we interviewed told us they broadened their clinical trial eligibility criteria and another manufacturer we interviewed reported that it was taking steps to do so. These two manufacturers told us they were taking these steps in part because both believe it will facilitate the drug approval process.³² Officials from one manufacturer stated that they broadened their eligibility criteria by removing exclusions after determining they were not critical to clinical trial designs, including exclusions related to liver function, infections (e.g., HIV), and the use of other medications (e.g., steroids). The officials explained that, since 2015, they have systematically evaluated their eligibility criteria to ensure that they do not unnecessarily exclude patient populations from their clinical trials. Officials from the second manufacturer told us they have begun evaluating whether to remove certain exclusion criteria that they typically use in clinical trials, and added that their efforts are partially in response to FDA's 2018 public workshop report, as described above. For example, the manufacturer is reviewing its exclusion of adolescents in prior clinical trials and officials told us they

³⁰See Pub. L. No. 115-52, § 610(a)(3), 131 Stat. 1052 (codified at 21 U.S.C. § 360bbb note). Food and Drug Administration, *Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs, Draft Guidance for Industry* (Silver Spring, Md.: June 2019).

³¹The draft guidance applies to both demographic populations (e.g., sex, race, age) and non-demographic populations (e.g., patients with organ dysfunction, comorbidities).

³²One manufacturer developing drugs to treat rare diseases stated that because of the small number of patients with such diseases, its eligibility criteria are sufficiently broad in order to recruit a large enough sample for a study.

will likely include adolescents in an upcoming study if they determine that patient safety would not be compromised.

Officials from both manufacturers stated that broader eligibility criteria will allow more patients to access investigational drugs through clinical trial participation. It can also, officials said, help them obtain FDA approval for a drug that extends to a wider range of patients, if the drug is found to be safe and effective. Further, officials from one of the two manufacturers noted that broader eligibility criteria, such as criteria that include patients with infections, could help streamline the process for conducting clinical trials—for example, by eliminating the need to conduct clinical testing to screen for the presence of infections.

Although most drug manufacturers in our review did not report efforts to broaden their eligibility criteria, many noted efforts to address other barriers to clinical trial participation. For example, to address geographic barriers, officials from six of the 10 manufacturers told us they help cover costs for patients to travel to clinical trial sites, such as by reimbursing transportation and hotel costs for patients who travel long distances.³³ In addition, officials from one manufacturer said they completed a pilot clinical trial on diabetes in 2019 that used decentralized trial locations in three states, such as retail health clinics and patients' homes, to help patients overcome challenges with obtaining transportation to trial sites. Similarly, within the next 2 years, another manufacturer is planning to conduct a pilot clinical trial that is fully remote and expects the design to improve patient participation in rural communities.

To address the lack of information about upcoming and ongoing clinical trials that is available to and tailored to patients, two manufacturers launched clinical trial registries in 2015 and 2016, respectively.³⁴ Officials from one of the manufacturers stated they designed their registry to bridge the gap between the information that patients want about clinical

³³According to FDA guidance, reimbursement for travel expenses to and from a clinical trial site and associated costs such as airfare and lodging do not raise issues of undue influence on the part of drug manufacturers and are generally considered acceptable practice. See Food and Drug Administration, *Information Sheet, Payment and Reimbursement to Research Subjects, Guidance for Institutional Review Boards and Clinical Investigators*, accessed June 18, 2019, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects>.

³⁴A clinical trial registry is a web-based search tool that helps patients locate information about ongoing clinical trials, including those conducted by manufacturers.

trials (e.g., information targeted to medical conditions that uses basic terminology), and what is available in ClinicalTrials.gov, a federal database that includes information on privately and publicly funded clinical trial studies.³⁵ Officials explained that ClinicalTrials.gov is, in general, more targeted to physicians.³⁶

In addition, to address barriers associated with the mistrust of research stemming from historical events among African-Americans and other communities, one manufacturer has several ongoing efforts to increase the participation of racially and ethnically diverse populations in its clinical trials.³⁷ For example, the manufacturer conducts workshops to train minority investigators who conduct clinical trials and requires certain clinical trial sites to be located in areas with minority patient populations of more than 25 percent.

Challenges with broadening eligibility criteria. Officials from four of the 10 drug manufacturers we interviewed—including the two taking steps to broaden their clinical trial eligibility criteria—told us broadening eligibility criteria is challenging. They stated that broader criteria must be carefully balanced with the need to collect evidence from a well-defined population. Officials from one manufacturer explained that removing standard exclusion criteria, such as excluding patients who use other medications, could interfere with the success of their clinical trial if those medications make it difficult to identify the effects of the studied drug. In addition, officials from another manufacturer emphasized that determining whether to remove exclusion criteria takes time and resources because it involves additional study, which could slow down the clinical development of a drug.

³⁵In addition to information about clinical trials, ClinicalTrials.gov includes certain information about the availability of expanded access for investigational drugs.

³⁶Officials from eight other stakeholders we interviewed similarly commented that ClinicalTrials.gov uses complex terminology, which can be difficult for some patients to understand.

³⁷There have been well-documented cases of abuse of African-American participants in clinical research, such as the Tuskegee Syphilis Study.

FDA Took Several Recent Actions to Facilitate Access to Investigational Drugs Outside of Clinical Trials

FDA Simplified the Institutional Review Board Process and Launched a Pilot Program to Facilitate Access to Investigational Drugs Outside of Clinical Trials

To facilitate access to investigational drugs outside of clinical trials, FDA has simplified its expanded access program's IRB review requirements for individual patient requests.³⁸ FDA made this change in October 2017, in accordance with a provision in FDARA.³⁹ This provision addressed concerns that FDA's requirement to convene a full IRB to review an expanded access request could result in delays of approvals because full IRBs may not meet regularly. Under the revised process, FDA now allows for a waiver of the requirement for full IRB review when concurrence is obtained by the IRB chair or another designated member. According to FDA officials, the updated process will help reduce the potential burden for physicians, who are responsible for obtaining IRB approval, while still protecting patients.

In addition, to further simplify its expanded access process for individual patient requests, in June 2019 FDA launched a pilot program called

³⁸See Food and Drug Administration, *Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers, Guidance for Industry* (Silver Spring, Md.: October 2017), 5-6.

Under FDA's expanded access program, a licensed physician can request access to investigational drugs for treatment use on behalf of a patient. FDA must approve the request, and if so, the request must be reviewed by an IRB. Our July 2017 report described actions FDA had taken to simplify the expanded access process, such as issuing a new simplified application form for individual requests and finalizing its related guidance.

FDA's expanded access program includes different processes for requests to access a drug for an individual patient and for requests to access a drug for multiple patients.

³⁹Pub. L. No. 115-52, § 610(b), 131 Stat.1053 (codified at 21 U.S.C. § 360bbb note).

Project Facilitate for oncologists and other health care professionals that treat patients with cancer.⁴⁰ According to FDA officials, the pilot program is focused on oncology because the agency receives a large number of individual expanded access requests from oncologists. Under the pilot program, FDA established a new call center that provides a single point of contact where FDA staff are available to answer questions, assist in filling out appropriate paperwork, and facilitate the overall process for requesting and obtaining access to investigational drugs. For example, FDA officials told us that FDA staff may assist oncologists in locating an IRB, if needed. As part of the pilot program, FDA will follow up on individual requests and gather data, such as how many patients received investigational drugs, and if not, why the requests were denied by manufacturers.⁴¹ According to FDA, the agency can use these data to determine how the process is benefiting patients.

Twenty of the stakeholders we interviewed were familiar with FDA's simplified IRB review requirements, and of those, 18 told us these updates were helpful for physicians and patients.⁴² For example, officials from one drug manufacturer commented that the new IRB review requirements reduce the amount of time it takes for patients to obtain access to investigational drugs, which is especially important for patients who are very sick. In addition, we spoke to 12 stakeholders about FDA's plans for its pilot program, and of those, nine generally had positive views of the agency's planned activities.⁴³ Officials from one manufacturer explained that the pilot program could help reduce the burden on oncologists seeking access to investigational drugs for their patients through the expanded access program. On the other hand, the officials from this same manufacturer raised concerns about the potential for FDA to intentionally or unintentionally pressure companies to make their investigational drugs available to patients, should FDA have increased involvement with drug manufacturers as part of the pilot program.

⁴⁰See Food and Drug Administration, *Project Facilitate*, accessed July 10, 2019, <https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate>.

⁴¹FDA officials told us the agency's current plan is to obtain such information from the treating physicians or their health care teams.

⁴²Of the 24 stakeholders, four were unfamiliar with the updates to the IRB review requirements.

⁴³Of the 24 stakeholders, we spoke to 12 about FDA's plans for its pilot program. We became aware of FDA's plans to conduct the pilot program after we completed many of our stakeholder interviews.

FDA Increased Communication about the Expanded Access Program and the Federal RTT Act to Facilitate Access to Investigational Drugs Outside of Clinical Trials

FDA has also taken recent actions to facilitate access to investigational drugs outside of clinical trials by increasing its communication about the expanded access program and the federal RTT Act.

FDA's increased communication about the expanded access program. In November 2018, FDA updated the web pages for its expanded access program in response to findings from an external assessment that the web pages were difficult to navigate and contained unclear information.⁴⁴ FDA created separate web pages for patients, physicians, and drug manufacturers, and tailored information about the expanded access process to each of these stakeholders. In addition, FDA added a new web page with information that is commonly requested by physicians and patients, such as the instructions for completing the form for submitting individual requests and definitions of keywords associated with the expanded access process (e.g., IRB, informed consent).

In addition, in October 2017, in response to a recommendation in our July 2017 report, FDA clarified its guidance for drug manufacturers on how the agency reviews adverse events that occur under FDA's expanded access program.⁴⁵ In the 2017 report, we found that some drug manufacturers were concerned that use of adverse event data may influence FDA in making final approval decisions, and that this possibility could contribute to a manufacturer deciding not to grant patients access to their drugs through the expanded access program. In response, we recommended that FDA clearly communicate how the agency will use adverse event

⁴⁴See Food and Drug Administration, *Expanded Access*, accessed May 29, 2019, <https://www.fda.gov/news-events/public-health-focus/expanded-access>.

To identify ways to improve its expanded access program, FDA commissioned an external assessment of the program in 2017 that included obtaining the perspectives of various stakeholders such as health care providers and drug manufacturers. See Food and Drug Administration, *Expanded Access Program Report* (Silver Spring, Md.: May 2018).

⁴⁵See Food and Drug Administration, *Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers, Guidance for Industry* (Silver Spring, Md.: October 2017), 18-19.

data from expanded access use when reviewing drugs and biologics for approval.⁴⁶

FDA's updated guidance states that FDA is not aware of instances in which adverse event information prevented the agency from approving a drug, and that it is very rare for FDA to place a clinical hold on an investigational drug due to adverse events observed during expanded access treatment.⁴⁷ The guidance also explains that several factors make it difficult for FDA to link an adverse event to the expanded use of a drug being considered for approval. For example, the guidance acknowledges that the use of investigational drugs through the expanded access program generally occurs outside of a controlled clinical trial setting and patients receiving such drugs may be sicker than patients participating in a clinical trial, making it more difficult to determine whether the use of the investigational drug has led to the adverse event.

In responding to questions about increased FDA communication about the expanded access program, 19 of the stakeholders we interviewed were familiar with FDA's updated expanded access web pages, and of those, 16 told us they were an improvement.⁴⁸ Officials from one physician organization stated that the updated web pages were easier to navigate than the previous web pages and presented information about the process more clearly.

Among the 10 manufacturers we interviewed, we found varying views of FDA's updated guidance on the use of adverse event data.

⁴⁶See [GAO-17-564](#).

⁴⁷For example, see study examining FDA's use of safety information obtained during expanded access to place clinical holds: Jonathan P. Jarow, Steven Lemery, Kevin Bugin, Sean Khozin, and Richard Moscicki, "Expanded Access of Investigational Drugs: The Experience of the Center of Drug Evaluation and Research Over a 10-Year Period," *Therapeutic Innovation & Regulatory Science*, vol. 50, no. 6 (2016). Also see study examining FDA's use of safety information obtained during expanded access to affect labeling: Jonathan P. Jarow and Richard Moscicki, "Impact of Expanded Access on FDA Regulatory Action and Product Labeling," *Therapeutic Innovation & Regulatory Science*, vol. 51, no. 6 (2017).

⁴⁸Of the 24 stakeholders, officials from three stakeholders told us they were unfamiliar with FDA's updated expanded access web pages. We did not ask the other two stakeholders their views on the updated web pages because of the timing of those interviews relative to the timing of FDA's updates.

- Officials from seven of the 10 manufacturers viewed the updated guidance as an improvement. Officials from one of the seven explained that it contributed to their company's decision to allow access to investigational drugs, when appropriate.
- Officials from two of the 10 manufacturers did not view the guidance as an improvement. Officials from both manufacturers stated that they still had significant concerns about the potential use of adverse event data by FDA to adversely affect the development of their investigational drugs, such as being used to issue a clinical hold. An official from one of the two manufacturers commented that these concerns remained despite FDA's statement in the guidance that it is difficult for FDA to link expanded access use to a particular adverse event. In addition, officials from two other manufacturers who viewed the guidance as an improvement similarly expressed remaining concerns that adverse events could negatively affect the development of their investigational drugs.
- One manufacturer was unfamiliar with the updated guidance.

Further, officials from four of the 10 drug manufacturers we interviewed, including two who viewed the updated guidance as an improvement, said they believed that manufacturers' concerns about this issue may never be fully resolved even with additional FDA guidance.

In other comments related to FDA's communication on its use of adverse events data from the expanded access program, some drug manufacturers we interviewed noted the merits of using efficacy and safety data from the expanded access program to inform FDA's drug approval decisions. Officials from two of the 10 manufacturers told us they believe that FDA's potential use of adverse event data from expanded access use, but not efficacy data, would be unfair. Officials from one of these two manufacturers cited FDA's updated guidance on adverse events as contributing to their view, referring to FDA's statement that it is unlikely that FDA's program would yield data that is useful to FDA in considering an investigational drug's effectiveness.

However, FDA officials told us that efficacy and safety data from the expanded access program have been used to support drug approvals in several instances. For example, in January 2018 FDA approved the drug Lutathera to treat rare tumors in the pancreas and gastrointestinal tract using efficacy and safety data the manufacturer submitted to FDA from a subset of the roughly 1,200 patients who received the drug through the expanded access program. Officials from four of the 10 manufacturers

expressed interest in discussing further with FDA how the agency would evaluate efficacy and safety data from the expanded access program and use these data to help support a drug's approval and other regulatory decisions.⁴⁹

FDA's communication about the federal RTT Act. In November 2018, FDA launched a new federal RTT web page that outlines both the eligibility requirements for patients interested in seeking access to investigational drugs and the criteria that must be met for an investigational drug to be eligible for use through this pathway.⁵⁰ For example, the web page states that patients must be diagnosed with a life-threatening disease or condition to be eligible to access investigational drugs under the federal RTT pathway. Further, the agency plans to issue proposed regulations in September 2019 to implement the federal RTT Act requirement for manufacturers to submit an annual summary to FDA on any use of their investigational drugs under this pathway.⁵¹ The regulations will include a due date for manufacturers to submit the annual summaries as well as information on what they are to contain, according to FDA.

Fourteen of the stakeholders we interviewed were familiar with FDA's new web page on the federal RTT Act, and among those, eight stated that it communicated useful and balanced information for physicians and patients.⁵² Officials from the remaining six stakeholders told us they did not find it helpful for physicians or patients. For example, officials from two stakeholders (including one drug manufacturer) commented at the

⁴⁹FDA officials told us they discussed the use of data from the expanded access program to support drug approval decisions at a November 2018 meeting that the Reagan-Udall Foundation sponsored for stakeholders, including drug manufacturers. See Reagan-Udall Foundation for the Food and Drug Administration, *Public Meeting Report: Leveraging Real-World Treatment Experience from Expanded Access Protocols* (Washington, D.C.: November 2018).

⁵⁰See Food and Drug Administration, *Right to Try*, accessed June 19, 2019, <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-to-try>.

⁵¹See Pub. L. No. 115-176, § 2(a), 132 Stat. 1372 (codified in pertinent part at 21 U.S.C. § 360bbb-0a(d)). This provision also requires FDA to post an annual summary report of the use of investigational drugs under the federal RTT pathway.

⁵²Of the remaining 10 stakeholders we interviewed, officials from seven stakeholders told us they were not familiar with the federal RTT web page. We did not ask the other three stakeholders their views on the federal RTT web page because of the timing of those interviews relative to the timing of the launch of the new web page.

time of our review that the web page could be misleading to some patients if they interpret the federal RTT Act to mean that manufacturers must provide access to their investigational drugs. Both added that FDA should more clearly communicate on the web page that there is no such requirement. In addition, officials from another stakeholder stated at the time of our review that FDA should explain on the web page the agency's role in implementing the federal RTT Act. In May 2019 FDA clarified on its web page that the federal RTT Act does not require manufacturers to provide patients access to their investigational drugs and that FDA's role includes posting a consolidated annual summary report on the use of investigational drugs through the federal RTT pathway.

Most Selected Manufacturers Communicated Whether They Consider Requests for Access to Investigational Drugs Outside of Clinical Trials and Conditions for Approval

Most of the 29 drug manufacturers in our review used their websites to communicate to patients and physicians whether they would consider individual requests for access to their investigational drugs outside of clinical trials. Among those that would consider requests, most also communicated the conditions under which they would review requests and grant access.

Manufacturers' consideration of requests for access. Our review of drug manufacturers' websites between January 31, 2019, and March 12, 2019, found that 23 of the 29 manufacturers in our review used their websites to communicate whether they considered individual requests for access to investigational drugs outside of clinical trials.⁵³ In communicating this information, 19 of the 23 manufacturers stated they were willing to consider requests, while the other four stated they were

⁵³Manufacturers used a variety of terms to characterize access to investigational drugs outside of clinical trials, such as "pre-approval access," "compassionate use access," and "early access."

not considering requests.⁵⁴ The remaining six of the 29 manufacturers did not communicate information about whether they would consider requests for access to investigational drugs outside of clinical trials at the time of our review, but officials from all six told us they were in the process of developing content on this topic that they intended to post on their websites.

Information communicated by manufacturers that consider requests. Among the 19 manufacturers willing to consider requests for access to investigational drugs outside of clinical trials, all communicated on their websites that they required physicians to submit requests on behalf of their patients and provided information on how physicians should submit these requests. In addition, 18 manufacturers communicated an estimated time frame within which they would respond to requests.⁵⁵ The manufacturers provided additional information, including the following:

- Eighteen communicated information about the type of patient for whom they would consider granting access.
 - Eighteen stated that patients must have a serious or life-threatening disease or condition; have no comparable or satisfactory alternative therapies available; and be unable to participate in a clinical trial to be eligible to obtain access.
 - In addition, 17 stated that the treating physician must determine for the patient seeking access that the risk of taking the investigational drug is not greater than the anticipated benefit.
- Fifteen communicated other factors they would take into account during their review of requests. These factors included the following:
 - Ten stated that the supply of their investigational drugs was a consideration. That is, a manufacturer must have a sufficient supply of the investigational drug to support the drug's clinical

⁵⁴Eleven of the 19 manufacturers that stated on their websites that they did consider requests for access also made this information available to patients and physicians on the Reagan-Udall Expanded Access Navigator. See Reagan-Udall Foundation, *Expanded Access Navigator Company Directory*, accessed April 2, 2019, <http://navigator.reaganudall.org/company-directory>.

⁵⁵The type of responses that drug manufacturers indicated they would give within these estimated time frames varied, including an acknowledgement of receipt and a decision about whether to provide access.

development before granting access to patients outside of clinical trials.

- Five referred to specific drugs to which they would consider granting access when describing the conditions under which they would consider reviewing requests. For example, one manufacturer stated that it would consider requests to access three of its investigational drugs (intended to treat bladder cancer, influenza, and HIV).
- One manufacturer communicated that after its initial review of individual requests, it uses an external advisory committee to further evaluate certain requests and ensure they are evaluated in an ethical and fair manner. The committee, which includes bioethical experts, physicians and patient representatives, makes recommendations to the manufacturer about providing access to individual patients.⁵⁶
- Many of the 19 manufacturers that communicated they were willing to consider individual requests for access stated that after they have approved a request they also required external entities to review the request. These included the following:
 - Thirteen stated they require the relevant regulatory authority to review requests. Of these, six specified that they require FDA to review requests for access in the United States. One of these six explained that it required a review by FDA to ensure all available safety data for the investigational drug were considered, and added that FDA is uniquely aware of such safety data.
 - Five stated they require the review of a research ethics committee or an IRB.⁵⁷

Information communicated by manufacturers that do not consider requests. Among the four manufacturers that communicated on their websites they were not considering requests for access to investigational drugs outside of clinical trials at the time of our review, two provided reasons for their decision. Both cited safety concerns; for example, one

⁵⁶In addition, this manufacturer communicated how many patients ultimately were granted access to an investigational drug outside of clinical trials. None of the other 18 manufacturers that communicated information about factors they take into account when reviewing requests also provided information on the number of patients for which they granted access to investigational drugs.

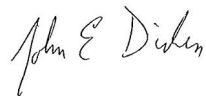
⁵⁷A research ethics committee is a group of individuals who undertake ethical review of research involving humans, applying agreed on ethical principles.

explained that it wanted to ensure its investigational drugs were administered to patients only through clinical trials where safety could be closely monitored. One also cited limited resources, stating that it chose to focus its resources solely on conducting clinical trials. Both of the manufacturers that provided reasons for not considering requests for access communicated that they will periodically re-evaluate their policies.

Agency Comments

We provided a draft of this report to HHS for comment and HHS provided technical comments, which we incorporated as appropriate. We are sending copies of this report to the appropriate congressional committees, the Secretary of the Department of Health and Human Services, and other interested parties. In addition, the report is available at no charge on the GAO website at <http://www.gao.gov>.

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



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Director, Health Care

Appendix I: GAO Contact and Staff Acknowledgments

GAO Contact

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

Staff Acknowledgments

In addition to the contact named above, Gerardine Brennan, Assistant Director; Pamela Dooley, Analyst-in-Charge; Craig Gertsch; Gay Hee Lee; and Moira Lenox made key contributions to this report. Also contributing were George Bogart, Laurie Pachter, and Ethiene Salgado-Rodriguez.

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