



July 2017

INVESTIGATIONAL NEW DRUGS

FDA Has Taken Steps
to Improve the
Expanded Access
Program but Should
Further Clarify How
Adverse Events Data
Are Used

Accessible Version

GAO Highlights

Highlights of [GAO-17-564](#), a report to congressional addressees

Why GAO Did This Study

FDA's goal for the expanded access program is to allow patients with immediately life-threatening and serious ailments access to investigational drugs when appropriate. Stakeholders have raised concerns that FDA's process is confusing or burdensome, particularly for the entities that have roles in the process—such as physicians, manufacturers, and institutional review boards.

GAO was asked to examine the expanded access program. Among other objectives, GAO examined 1) what is known about the number, type, and time frames of expanded access requests received by FDA; 2) what actions FDA and other stakeholders have taken to improve expanded access; and 3) how FDA uses data from expanded access in the drug approval process.

GAO reviewed regulations and FDA documents and analyzed FDA data on the numbers and types of expanded access requests it received from FY2012 through 2015, the most recent at the time of the review. GAO also interviewed FDA officials and other stakeholders including nine manufacturers—selected to represent large and small companies—and patient and physician representatives.

What GAO Recommends

FDA should clearly communicate how it uses adverse events data from expanded access use in the drug approval process. FDA agreed with the recommendation.

View [GAO-17-564](#). For more information, contact John Dicken at (202) 512-7114 or Dickenj@gao.gov.

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Investigational New Drugs

FDA Has Taken Steps to Improve the Expanded Access Program but Should Further Clarify How Adverse Events Data Are Used

What GAO Found

Under the Food and Drug Administration's (FDA) expanded access program, patients with serious or life threatening ailments and no other comparable medical options can obtain access to investigational drugs outside of a clinical trial. Expanded access requests must be submitted to FDA but manufacturers must also grant permission for patients to access their investigational drugs. Of the nearly 5,800 expanded access requests that were submitted to FDA from fiscal year 2012 through 2015, FDA allowed 99 percent to proceed. Almost 96 percent of these requests were for single patients (either emergency or non-emergency). FDA's review process for expanded access requests is designed such that all requests are either allowed or not allowed to proceed within 30 days of receiving each request. FDA typically responded to emergency single-patient requests within hours and other types of requests within the allotted 30 days.

FDA and other stakeholders, including a non-profit organization and a drug manufacturer, have taken steps to improve the expanded access process and patient access to drugs. For example, in response to concerns that the process to request expanded access to drugs was complex and cumbersome, FDA simplified its website, guidance, and the forms required for the most common types of requests. Efforts by other stakeholders include a project to educate and streamline the process by which institutional review boards approve treatment plans for expanded access drug use and a pilot advisory group to help a drug manufacturer manage expanded access requests. Some states have also enacted "Right-to-Try" laws to facilitate patient access to investigational drugs. These laws provide liability and licensing protections for manufacturers and providers under state law if an adverse event—such as an adverse reaction to the drug—occurs with patients who were allowed access to investigational drugs. However, some stakeholders GAO interviewed cited concerns that these laws may not help patients access drugs, in part because they do not compel a manufacturer to provide access.

Manufacturers sponsoring clinical trials must submit safety reports to FDA that include adverse events data resulting from clinical trials and any expanded access use, to be used in assessing the safety of a drug within the drug approval process. FDA reported using these data from expanded access use in a few cases during the drug approval process but not more widely, because its use does not have the same controls as clinical trials. FDA officials reported that they communicate with manufacturers on how they will use expanded access adverse events data. However, GAO's review of documents FDA uses to communicate with drug manufacturers about the expanded access program found that only one included a reference to its use of these data, and it did not include specific examples of how the data might be used. Further, some of the manufacturers told GAO the guidance was unclear. These manufacturers noted that the lack of clear information can influence their decision whether to give patients access to their drugs because of their concerns that an adverse event will result in FDA placing a clinical hold on their drug, which could delay its development. This could impact FDA's goal of facilitating expanded access to drugs for treatment use by patients with serious or life-threatening diseases or conditions, when appropriate.

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Abbreviations

BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CompAC	Compassionate Use Advisory Committee
FDA	Food and Drug Administration
IND	investigational new drug application
IRB	institutional review board
NDA	new drug application
NYU	New York University

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July 11, 2017

Congressional Addressees

Through the Food and Drug Administration’s (FDA) expanded access program, patients with serious or immediately life-threatening ailments and no other FDA-approved therapeutic options may potentially obtain investigational drugs or biologics as a last resort for treatment.¹ In these instances, FDA may allow access to treatments using drugs still in the development process—and, therefore, not yet approved by FDA for marketing in the United States—when certain criteria are met. In addition to FDA—which receives and reviews expanded access requests and determines whether to allow them to proceed—other entities have roles in the process.² For example, manufacturers decide whether to give patients access to their investigational drugs. In addition, institutional review boards (IRB) must approve patients’ expanded access treatment plans, and physicians treat the patients with the investigational drugs and monitor their progress.

FDA has reported that it allows nearly all of the expanded access requests it receives to proceed; however, little is known about the number of requests denied by manufacturers and, therefore, never submitted to FDA. In addition, little is known about the time it takes FDA to review expanded access requests—although, in most cases, expanded access use may begin 30 days after the request is received by FDA, unless the agency acts to expedite or disallow the request from proceeding.³

¹Investigational drugs and biological products have not been approved for marketing in the United States by FDA. See 21 C.F.R. § 312.3 (2016). 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). Biological products are materials, such as viruses, therapeutic sera, toxins, antitoxins, vaccines, or analogous products to prevent, treat, or cure human diseases or injuries. See 42 U.S.C. § 262(i) (2016) and 21 C.F.R. § 600.3(h) (2016). For the purpose of this report we refer to drugs and biologics collectively as “drugs.” In general, biological products are derived from living sources, such as humans, animals, and microorganisms.

²By allowing an expanded access request to proceed, FDA is authorizing the expanded access use of a drug for treatment, subject to other program requirements.

³See 21 C.F.R. § 312.305(d) (2016).

FDA's expanded access program has been criticized by some physician and patient advocacy groups for being too burdensome and confusing to the entities involved, which could pose a barrier to individuals' access to investigational drugs. Additionally, manufacturers have raised concerns about how FDA might use data from expanded access use in its process for approving the drug for marketing in the United States. However, stakeholders, including physicians, patients, and patient advocates, have also highlighted steps FDA and other stakeholders have taken to improve the program.

You asked us to review various aspects of FDA's expanded access program. This report examines

1. what is known about the number, type, and time frames of expanded access requests that are allowed to proceed by selected drug manufacturers and by FDA;
2. what factors selected drug manufacturers and FDA consider when reviewing expanded access requests;
3. what actions FDA and other stakeholders have taken to improve expanded access; and
4. how, if at all, FDA has used data from expanded access use in its drug approval process.

To determine what is known about the number, type, and time frames of expanded access requests that are allowed to proceed, we analyzed information collected through interviews or written responses to questions from a non-generalizable selection of nine drug manufacturers on their experiences with the expanded access program. The manufacturers were selected to include large and small manufacturers based on the number of FDA approved products they were marketing as well as other factors, such as whether they had experience with the expanded access program.⁴ Additionally, we obtained and analyzed data from FDA on the number, type, and time frames of expanded access requests reviewed by

⁴Among the nine manufacturers, we selected the following from information from a manufacturer trade group's membership list: four were identified by the trade group as being established companies marketing multiple drugs, and two were identified as small companies, either not yet marketing any drugs or just beginning to market drugs. Of the additional manufacturers, two were selected because they were known for having experience with expanded access and self-identified as established companies that were marketing multiple biologics, and one was selected because it is publically known to have experience with expanded access and self-identified as a small company developing biologics.

the agency from fiscal year 2012 through fiscal year 2015.⁵ To assess the reliability of FDA's data, we interviewed knowledgeable agency officials, conducted quality checks to identify any obvious errors, and compared the detailed data FDA provided to us with summary data that FDA had publicly reported on its website. We determined these data were sufficiently reliable for the purposes of our reporting objective.

To describe the factors that manufacturers and FDA take into account when reviewing expanded access requests, we analyzed information collected through interviews or written responses from the nine selected manufacturers. Additionally, we reviewed FDA regulations pertaining to expanded access to investigational drugs and interviewed knowledgeable FDA officials.⁶

To determine the actions that FDA and other stakeholders have taken to improve expanded access, we reviewed FDA regulations and guidance related to expanded access and interviewed knowledgeable FDA officials. We also analyzed information collected through interviews with or written responses from the 9 manufacturers and a non-generalizable selection of 14 other stakeholders, including patient and physician advocacy groups, and analyzed publically available proposals and reports regarding efforts to improve expanded access.⁷

To evaluate how FDA has used data from expanded access use in its drug approval process, we analyzed information from interviews with FDA and the stakeholders. Lastly, we assessed FDA's communication with manufacturers on the agency's use of expanded access data against the federal internal control standards related to information and communication.⁸ The forms of communication we reviewed included FDA's regulations, guidance documents, and website and other forms of communication with manufacturers regarding expanded access, such as letters acknowledging the receipt of expanded access requests.

⁵Fiscal year 2015 was the most recent year of data available when we conducted our work.

⁶See 21 C.F.R. pt. 312, subpt. I, §§ 312.300 et seq. (2016).

⁷These 14 other stakeholders included patient and physician representatives, as well as individuals or organizations identified by FDA and others as stakeholders who were knowledgeable about the expanded access program.

⁸See GAO, *Standards for Internal Control in the Federal Government*, GAO-14-704G (Washington, D.C.: September 2014)

We conducted this performance audit from March 2016 to June 2017 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

FDA is responsible for assessing the safety, efficacy, and quality of drugs marketed in the United States. As part of this role, it oversees the drug development process and is responsible for approving new drugs for marketing. Patients with serious or immediately life-threatening illnesses and no other FDA-approved therapeutic options may be able to access treatments still in the development process through FDA's expanded access program.

Drug Development and Approval Process

The process by which a drug or biologic is developed and considered for approval for marketing in the United States involves a number of steps that include the clinical testing of the drug's safety and effectiveness on human volunteers. Before a drug can be tested on humans, it is first tested for toxicity on animals. Following such testing, a manufacturer must submit an investigational new drug application (IND) to FDA in order to test the drug on humans. FDA's decision of whether or not to allow the human testing to proceed is based, in part, on evidence and analysis regarding the drug's toxicity in animals and the availability of human volunteers. Additional information about the typical process for human testing and FDA's review processes is described below and depicted in figure 1.⁹

Pre-clinical Testing

Before a drug or biologic can be tested on humans, it is tested for toxicity on animals. These tests are also used to gather basic information on the

⁹A clinical trial tests potential drugs or biologics in human volunteers to determine if they should be approved for wider use in the general population.

safety and efficacy of the drug or biologic. FDA may decide whether or not to allow the investigational drug to be tested on humans, based in part on results of the drug being tested on animals.

Investigational New Drug Application

A manufacturer that wants to test an investigational drug or biologic on humans must first submit an IND to FDA for the agency to review, and FDA must allow the IND to proceed before testing on humans can begin.¹⁰ The IND includes various components, such as the clinical treatment plan, which provides the detailed procedure for how humans will be tested, and Form FDA 1571, which contains a number of administrative elements pertaining to the request. See appendix I for a copy of this form.

Clinical trials on humans can only begin after FDA has reviewed and allowed the application to proceed and an IRB has reviewed and approved the clinical treatment plan and reviewed the patient's informed consent form.¹¹ After receiving this approval, the manufacturer is considered the sponsor of an existing IND, and clinical trials that involve human volunteers can begin. Once in effect, the sponsor of the existing IND may amend its research plan as needed, such as to expand or otherwise change patient eligibility criteria. Testing under an amended treatment plan may only begin after the changes have been submitted to FDA and approved by an IRB.

Clinical Trials

An investigational drug typically goes through three phases of clinical trials before it is submitted to FDA for marketing approval. According to FDA officials, in some cases when a new drug is being tested for a life-threatening ailment, the drug development process may be expedited by

¹⁰See 21 C.F.R. pt. 312, subpt. B, §§ 312.20 et seq. (2016).

¹¹The IRB's role is to ensure protections for human volunteers in clinical trials and that informed consent will be obtained. According to FDA, an IRB means 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. Many 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. An IRB generally incurs costs for their review of expanded access requests and may charge physicians or others for reviews.

going through only one or two phases of clinical trials before an application is submitted to FDA for marketing approval. At any point during the clinical trials, FDA could issue a clinical hold on the existing IND that would delay the proposed or ongoing clinical trials.¹² When a drug undergoing clinical trials is placed on clinical hold, it cannot be administered to any human volunteers. This includes volunteers already in a clinical trial, and no new volunteers may be recruited to clinical trials. If the drug completes a clinical trial phase and is not on clinical hold, FDA allows it to proceed to the next phase. The three clinical trial phases are detailed below:

- **Phase I:** Phase I clinical trials generally test 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:** Phase II clinical trials assess the drug's safety and effectiveness on people who have a certain disease or condition and typically are conducted on a few dozen to hundreds of volunteers. 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:** Phase III clinical trials generally involve several hundreds to thousands of volunteers and gather more information about the drug's safety and effectiveness on different patient populations and at different dosages, 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.

Review and Approval Process

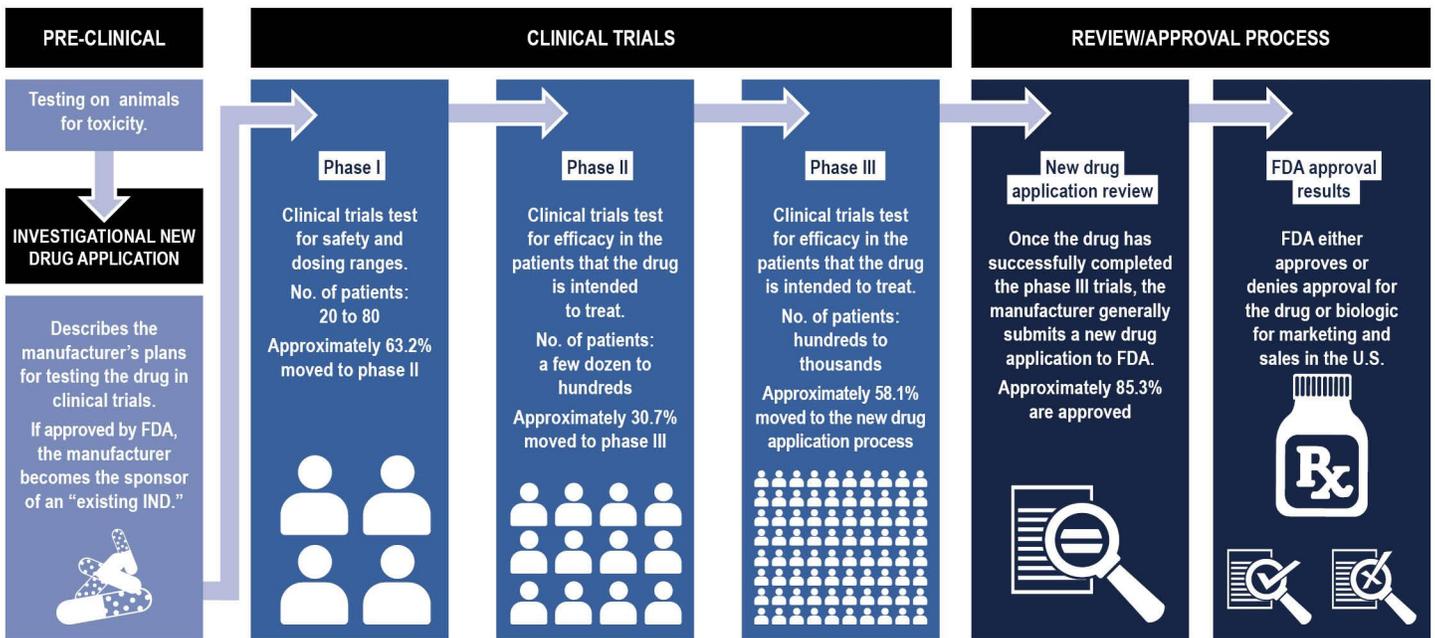
When seeking FDA's approval to market and sell a drug in the United States, the manufacturer submits an application to FDA.¹³ Included in these submissions are the data from the safety and efficacy clinical trials

¹²Reasons for imposing clinical holds can include human volunteers being subject to unreasonable and significant risks of illness or injury.

¹³When seeking approval for marketing of a new drug in the United States, the manufacturer submits to FDA a new drug application (NDA). See 21 C.F.R. § 314.50 (2016). When seeking approval for marketing of new biologic in the United States, the manufacturer submits to FDA a biologics license application (BLA). See 21 C.F.R. § 601.2 (2016).

for FDA to review. FDA uses the information in the application to either approve or not approve the drug. Based on a study looking at 10 years of data, among the drugs that enter Phase I clinical trials, on average, 9.6 percent were ultimately approved for marketing in the United States.¹⁴ For example, if 100 investigational drugs entered Phase I clinical trials, approximately 63 (63.2%) would advance to Phase II clinical trials, with 19 of those (30.7%) advancing to Phase III clinical trials. Of those 19 drugs, 11 (58.1%) would advance to the new drug application process, and, ultimately, 10 of those (85.3%) would be approved for marketing and sale in the United States.

Figure 1: Food and Drug Administration’s (FDA) Typical Drug Development and Approval Process



Source: GAO analysis of FDA data and a 2016 collaborative study by Biotechnology Innovation Organization, Biomedtracker, and Amplion.^a | GAO-17-564

Note: According to FDA officials, there can be wide variation in the number of patients involved in the different clinical trial phases, and, when a new drug is being tested for a life-threatening ailment, 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.

^aDavid W. Thomas et al., *Clinical Development Success Rates 2006-2015* (Washington, D.C.: BIO, 2016).

¹⁴David W. Thomas et al., *Clinical Development Success Rates 2006-2015* (Washington, D.C.: BIO, 2016).

Expanded Access Program

Through FDA's expanded access program, licensed physicians, on behalf of their patients with serious or immediately life-threatening ailments, who have no other comparable medical options, and who are unable to participate in a clinical trial, can request and possibly access investigational drugs for treatment of the patients, if the patients meet certain eligibility requirements.¹⁵ 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. All expanded access requests must be submitted to FDA, and once received take effect within a designated time unless the agency acts to expedite or disallow them from proceeding. The expanded access process also requires the involvement of other entities, including the manufacturer that is developing the drug and must provide access to it, an IRB that must approve the expanded access treatment plan and review the patient's informed consent form, and a physician who administers the drug. FDA categorizes expanded access requests into two broad categories—protocol requests and IND requests—and the roles and responsibilities of each of these entities within the process can vary depending on the category of the request.

Expanded Access Protocol Requests

An expanded access protocol request aims to provide access to an investigational drug outside of a clinical trial when the sponsor of an existing IND submits a treatment plan for expanded access in an amendment to that existing IND. The manufacturer typically makes these requests and is, therefore, the sponsor of the expanded access request. The manufacturer must submit the expanded access treatment plan using a new Form FDA 1571 notifying FDA that the manufacturer is amending its existing IND to provide the investigational drug to one or more patients outside of the clinical trial. An expanded access protocol may be submitted to provide access to a single patient or to more than one patient. A manufacturer may decide to open an expanded access protocol because it has received requests for a drug that is still in clinical trials—for example, requests for terminal patients with no other options—or

¹⁵FDA's expanded access eligibility requirements are outlined in FDA's regulations on expanded access to investigational drugs, 21 C.F.R. pt. 312, subpt. I, §§ 312.300 et seq. (2016).

because it has a drug that has completed clinical trials and wants to make the drug available to patients who have no other comparable treatment options while waiting for FDA's new drug approval response. For expanded access protocol requests sponsored by manufacturers, the roles and responsibilities of the various entities involved in the process typically are as follows:¹⁶

- **The manufacturer:** In addition to submitting the request for the expanded access protocol to FDA, the manufacturer, as the sponsor of the request, is responsible for the collection and submission of data to FDA on any adverse events that occurred from administering the drug to patients who received it under the expanded access protocol. These data are included with the manufacturer's regular adverse event data reporting to FDA under the existing IND.
- **The physician:** The patient's physician administers the investigational drug to the patient and must report any serious adverse events to the manufacturer sponsoring the expanded access protocol.
- **The IRB:** A designated IRB must approve the clinical treatment plan that is submitted as part of the expanded access protocol application (similar to its review of the original clinical treatment plan) and review the patient's informed consent form. FDA generally requires that all IRB reviews be completed by a full IRB—meaning the majority of members of the board participate in the review process—and FDA makes no specific exception for expanded access.¹⁷

Expanded Access IND Requests

An expanded access IND request aims to provide access to an investigational drug outside of a clinical trial and under a new IND. The vast majority of expanded access IND requests are opened to provide access to a single patient.¹⁸ A patient's physician typically submits these

¹⁶Sponsors of expanded access protocol requests can also be a physician or a third party, such as an academic institution, but more typically are manufacturers.

¹⁷See 21 C.F.R. § 56.108(c) (2016). Expedited review procedure does not require full IRB review. Also, emergency use applications are exempted from prospective IRB review altogether, although emergency expanded access use must still be reported to the IRB within five working days. See 21 C.F.R. §104(c) (2016).

¹⁸IND requests for multiple patients are often requested by manufacturers and require the submission of Form FDA 1571 to FDA.

single-patient requests and is, therefore, the sponsor of these requests and must submit to FDA the Individual Patient Expanded Access Application, using Form FDA 3926 or Form FDA 1571.¹⁹ See appendix II and appendix I for copies of these forms. In general, physicians would pursue expanded access IND requests when they learn of a drug being developed and think the benefit of giving their patient expanded access outweighs the risks. For expanded access IND requests sponsored by physicians, the roles and responsibilities of the various entities involved in the process typically are as follows:²⁰

- **The physician:** The physician first obtains a letter of authorization from the manufacturer that documents it will allow the physician to reference its existing IND information. After receiving this letter, the physician submits an expanded access request to FDA. If FDA allows the request to proceed to treatment, the physician must provide FDA with a written summary of the results at the conclusion of treatment.
- **The manufacturer:** The manufacturer decides whether it will allow the patient (or patients) access to the drug. If the manufacturer decides to give the patient (or patients) access to the drug, it gives the physician a letter of authorization.
- **The IRB:** The IRB must approve the clinical treatment plan that is submitted as part of the expanded access IND application and review a patient's informed consent form.²¹ FDA generally requires that all IRB reviews be completed by a full IRB—meaning the majority of the members of the board participate in the review process—and FDA makes no specific exception for expanded access.²²

¹⁹The Individual Patient Expanded Access Application, Form FDA 3926, was finalized in June 2016, along with related guidance documents for industry: *Individual Patient Expanded Access Application: Form 3926*; *Expanded Access to Investigational Drugs for Treatment use—Questions and Answers: Guidance for Industry*; and *Charging for Investigational Drugs Under an IND—Questions and Answers: Guidance for Industry*.

²⁰For expanded access IND requests sponsored by manufacturers, the roles and responsibilities of the various entities involved in the process are similar to those for expanded access protocol requests. Likewise, for expanded access protocol requests sponsored by physicians, the roles and responsibilities of the various entities involved in the process are similar to those for the expanded access IND requests.

²¹See 21 C.F.R. § 312.305(c)(4) (2016).

²²See 21 C.F.R. § 56.108(c) (2016). Expedited review procedure does not require full IRB review. Also, emergency use applications are exempted from prospective IRB review altogether, although emergency expanded access use must still be reported to the IRB within five working days. See 21 C.F.R. § 104(c) (2016).

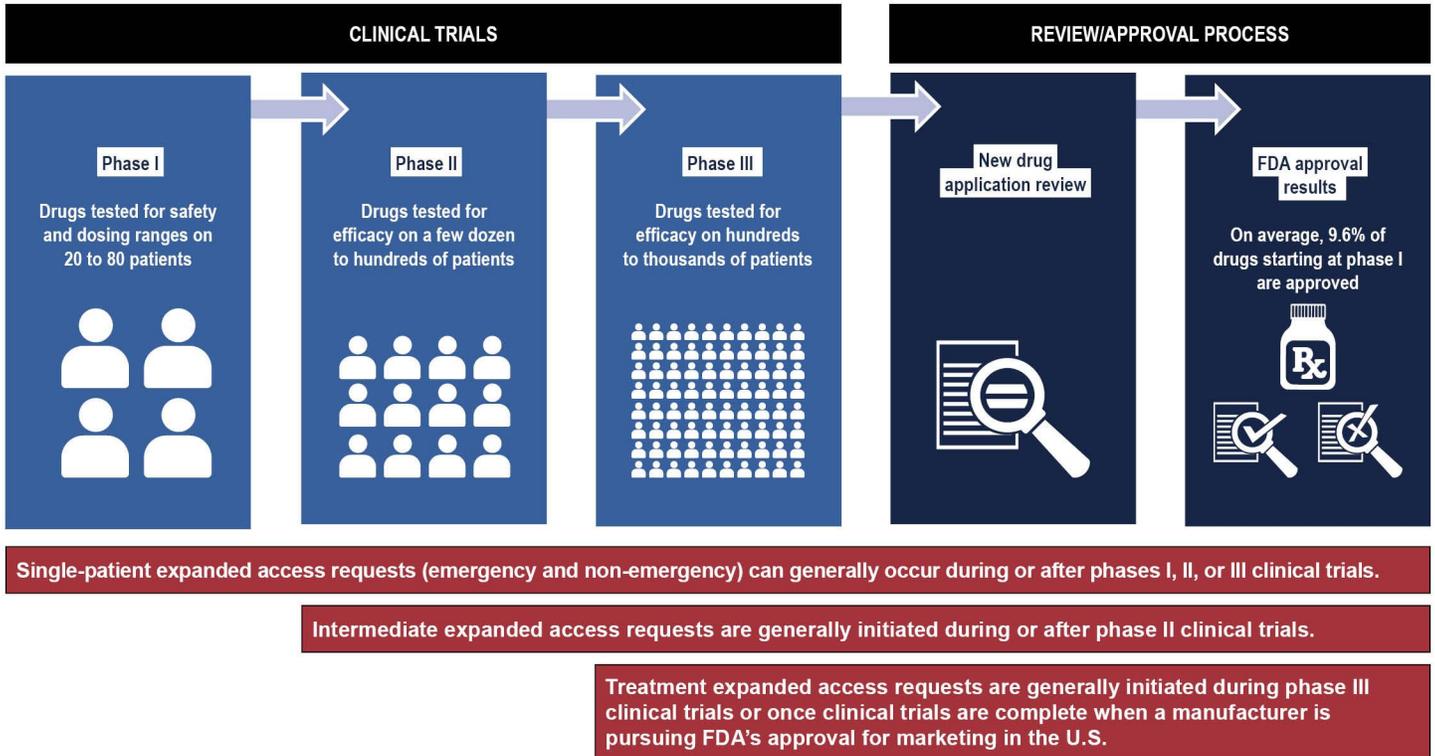
Beyond these broad categories, FDA further categorizes expanded access requests (whether protocol or IND requests) by the number of patients treated and the type of situation. The agency reports data separately on four categories of expanded access requests that FDA defines as follows:

1. Single-patient.
2. Single-patient emergency, for example, for a patient who is not expected to live long enough for FDA and an IRB to review a typical single-patient expanded access request.²³
3. Intermediate-size generally for two patients to potentially hundreds of patients.
4. Treatment for larger widespread populations.

Where the drug is at in the drug development process can affect the type of expanded access request that may be submitted to FDA. (See figure 2.)

²³Emergency requests are generally received and authorized by FDA over the telephone. If approved, the physician must submit an expanded access submission to FDA within 15 business days and notify an IRB within 5 business days of the emergency use.

Figure 2: Types of Expanded Access Requests that Occur throughout the Food and Drug Administration’s (FDA) Typical Drug Development and Approval Process



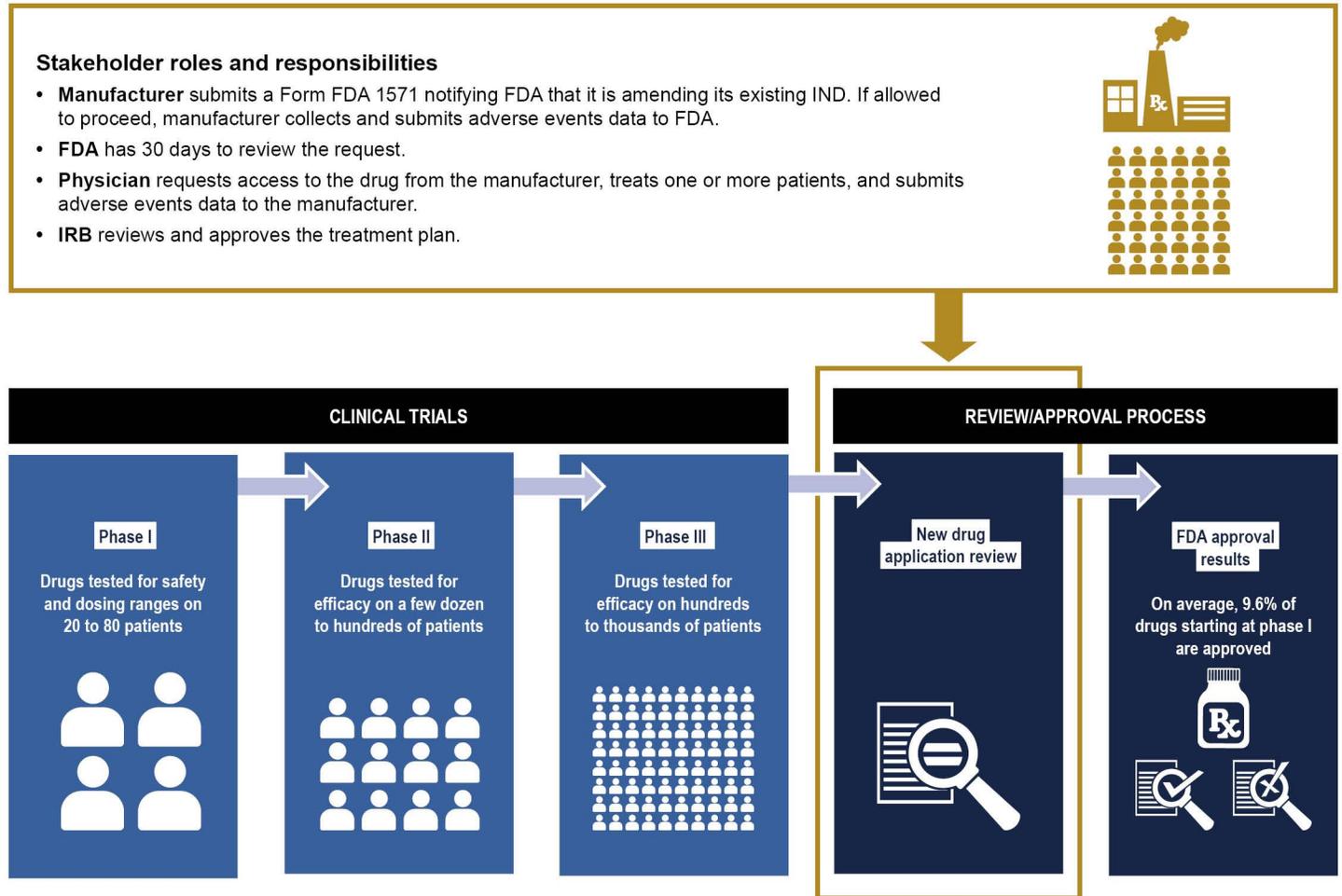
Source: GAO analysis of FDA data. | GAO-17-564

Note: According to FDA officials, there can be wide variation in the number of patients involved in the different clinical trial phases, and, when a new drug is being tested for a life-threatening ailment, 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.

Figures 3 and 4 illustrate two common examples of situations in which expanded access requests may be submitted to FDA and the roles and responsibilities of various stakeholders for each example. They include an example of an expanded access treatment protocol request submitted by a manufacturer late in the drug development process, and an expanded access single-patient IND request submitted by a physician earlier in the process.

Figure 3: Expanded Access Treatment Protocol Example

A manufacturer's drug was successful in clinical trials. The manufacturer is pursuing approval from Food and Drug Administration (FDA) to sell and market the drug in the United States. While waiting for FDA's approval decision, the manufacturer would like to set up an expanded access protocol so that a large number of terminal patients can access the drug.



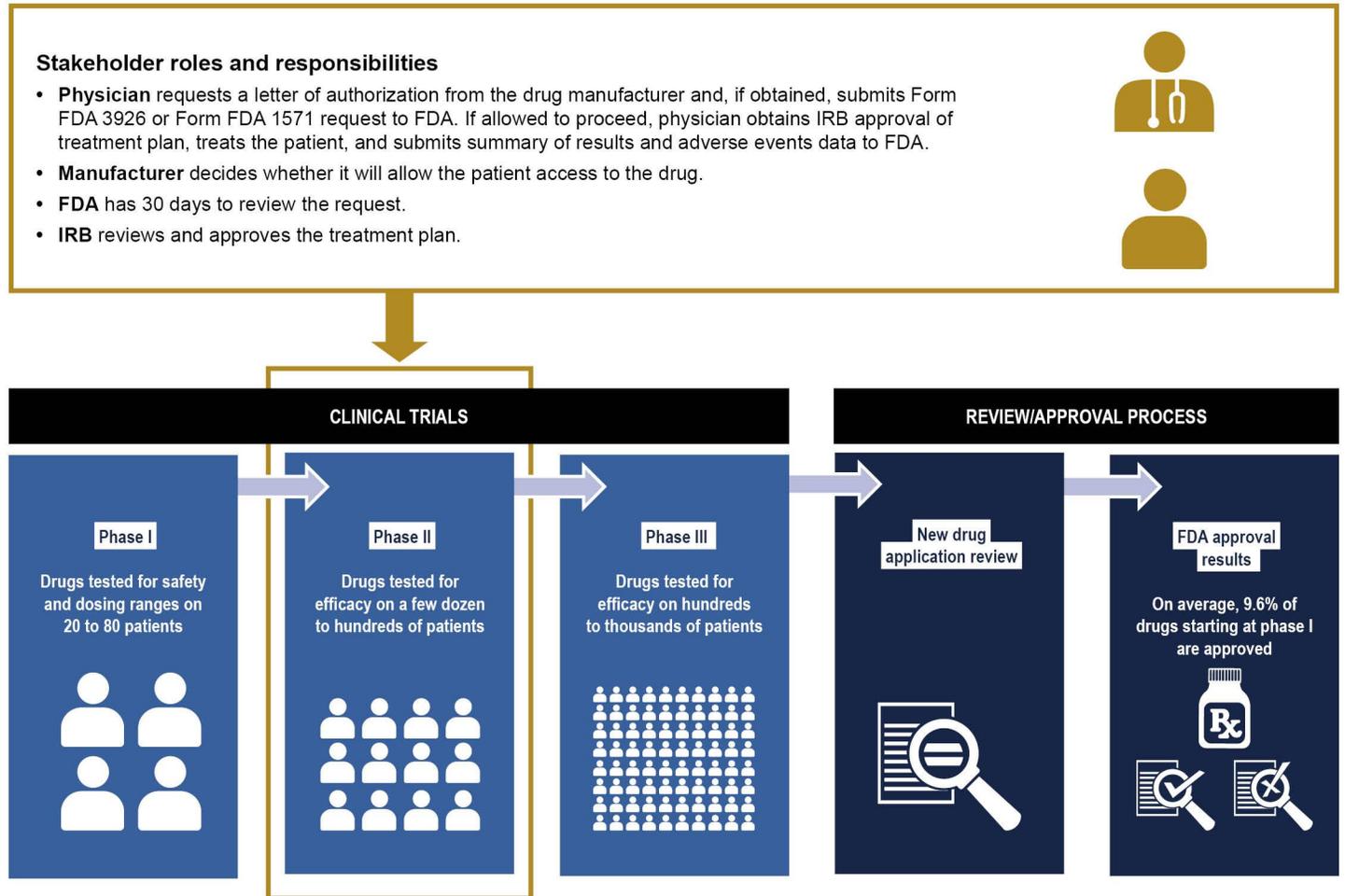
Legend: FDA= Food and Drug Administration; IRB= institutional review board.

Source: GAO analysis of FDA data. | GAO-17-564

Note: According to FDA officials, there can be wide variation in the number of patients involved in the different clinical trial phases, and, when a new drug is being tested for a life-threatening ailment, 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.

Figure 4: Expanded Access Single-Patient IND Example

A physician learns of a promising drug being developed that has just started phase II clinical trials. The physician would like to sponsor a single-patient IND for her terminal patient.



Legend: FDA= Food and Drug Administration; IRB= institutional review board.

Source: GAO analysis of FDA data. | GAO-17-564

Note: According to FDA officials, there can be wide variation in the number of patients involved in the different clinical trial phases, and, when a new drug is being tested for a life-threatening ailment, 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.

Within FDA, the centers that oversee the pre-clinical and clinical testing of drugs and biologics, the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), also review and determine whether an expanded access request for a drug or biologic is allowed to proceed.²⁴

Selected Drug Manufacturers Reported Different Experiences with Expanded Access Requests, and FDA Allowed Nearly All Requests to Proceed from Fiscal Year 2012 through 2015

Selected Drug Manufacturers Reported Different Experiences with the Number and Types of Expanded Access Requests They Received

Each of the nine selected manufacturers from whom we obtained information reported having experiences with the expanded access program, but the extent of the experiences, and with what type of request, varied. Specifically,

- one manufacturer reported only having experience with expanded access IND requests;
- three manufacturers reported only having experience with expanded access protocol requests; and
- five manufacturers reported having experience with both types of requests.

Of those manufacturers that had experience with expanded access IND requests, all of the requests were sponsored by physicians and were for single patients, including both emergency and non-emergency requests. Most of these manufacturers said that expanded access INDs can happen at any phase of a drug's development, but, based upon the availability of safety and efficacy data, manufacturers are more likely to

²⁴Within CDER, there are 16 divisions that review expanded access requests, based upon a drug's therapeutic indication; similarly, within CBER, there are 3 offices that review expanded access requests.

approve these requests at later phases of drug development. The numbers of single-patient IND requests these manufacturers reported receiving ranged from 39 to approximately 800. Additionally, some manufacturers reporting experience with expanded access IND requests said that they may decide to establish an expanded access protocol instead of separately considering single-patient expanded access IND requests. For example, one manufacturer reported that, once it receives an expanded access IND request for a single patient, it will proactively evaluate whether there is the potential for additional requests, and, if so, it will work to establish an expanded access protocol to cover a group of patients for FDA's review. Another manufacturer said that it has three pathways for patients to access investigational drugs—clinical trials, expanded access protocols, and expanded access INDs—and that it will first evaluate whether a patient is eligible for its clinical trial or an expanded access protocol it has established before it will consider providing access to the drug through an expanded access IND request.

Three of the nine selected manufacturers reported that their only experience with the expanded access program was with expanded access protocol requests. These manufacturers cited the following reasons for establishing expanded access protocols. One reason cited by two manufacturers was that expanded access protocols allowed them to give groups of patients access to their drugs subsequent to completion of their phase III clinical trials, pending approval of their drug for marketing. Another manufacturer said that it had already built late-phase expanded access into its overall drug development plans. Among these manufacturers, the reported numbers of patients covered under their expanded access protocols varied—ranging from 18 patients to 800 patients.

FDA Allowed 99 Percent of Nearly 5,800 Expanded Access Requests to Proceed During Fiscal Years 2012 through 2015

From fiscal year 2012 through 2015, FDA reviewed nearly 5,800 expanded access requests and allowed nearly all of them to proceed. Specifically, of the 5,753 expanded access requests the agency reviewed, it allowed 5,697 (99 percent) to proceed.²⁵ (See table 1.) According to a study using FDA data, in the rare cases when FDA did not allow a request to proceed, the most common reasons were incomplete applications, unsafe dosing, the requested drug’s demonstrated lack of efficacy for its intended use, the availability of adequate alternative therapies, and inadequate information provided in the application on which to base a decision.²⁶

Table 1: Total Expanded Access Requests Reviewed and Allowed to Proceed by Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, by Type, Fiscal Years 2012 through 2015

Type of request	Type of request	Number reviewed	Allowed to proceed	Percent allowed to proceed
Single-patient	Emergency	2,451	2,436	99.4
Single-patient	Non-emergency	3,047	3,016	99.0
Multiple patients	Intermediate-size	204	194	95.1
Multiple patients	Treatment (widespread)	51	51	100.0
Total	n/a	5,753	5,697	99.0

Source: GAO analysis of FDA data | GAO-17-564

Note: This table includes both expanded access IND requests and expanded access protocol requests.

Nearly all of the expanded access requests FDA received and reviewed (approximately 96 percent) were for single patients (including both emergency and non-emergency requests). However, because intermediate-size and treatment requests expand access to groups of patients, more patients may have gained expanded access to drugs

²⁵These data only reflect information on requests that were submitted to FDA. The physician also must obtain authorization from the manufacturer to access the drug, which typically is obtained before the physician submits a request to FDA.

²⁶Jonathan P. Jarow, Steven Lemery, Kevin Bugin, and Naomi Lowy, “Ten-Year Experience for the Center for Drug Evaluation and Research, Part 2: FDA’s Role in Ensuring Patient Safety,” *Therapeutic Innovation & Regulatory Science*, vol. 51, no. 2 (2016).

through these types of requests. For example, one of the selected manufacturers reported that 400 patients received its drug through an expanded access treatment protocol and anticipated further growth in the number of patients treated under that protocol by the end of 2016. Another manufacturer reported that over 1,500 patients had requested access to its treatment protocol since November 2015. FDA officials said that the agency does not keep data on the number of patients treated under intermediate-size or treatment expanded access requests.

We analyzed data from the FDA divisions and offices that reviewed expanded access requests and found that most requests were concentrated among a few divisions and offices. For example, among the 16 CDER divisions that review these requests, four divisions—Anti-infective, Antiviral, Hematology, and Oncology 2—reviewed over 3,700 requests, accounting for 74 percent of all requests that CDER received from fiscal year 2012 through 2015. In contrast, during that same time period 9 other divisions reviewed a combined total of 201 requests, accounting for 4 percent of all requests received. (See table 2.)

Table 2: Number of Expanded Access Requests Reviewed by Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER), by Division and Type of Request, Fiscal Years 2012 through 2015

Division	Single-patient		Multiple patients		Total	Percent
	Emergency	Non-emergency	Intermediate-size	Treatment (widespread)		
Anti-infective	261	1,031	4	0	1,296	25.6
Antiviral	911	70	2	0	983	19.4
Hematology	466	406	12	8	892	17.6
Oncology 2	20	521	14	15	570	11.3
Gastroenterology and Inborn Errors of Metabolism	291	124	52	2	469	9.3
Oncology 1	39	398	2	3	442	8.7
Neurology	60	88	58	2	208	4.1
All other divisions ^a	74	85	30	12	201	4.0
Total	2,122	2,723	174	42	5,061	100.0

Source: GAO analysis of FDA data. | GAO-17-564

Note: This table includes both expanded access IND requests and expanded access protocol requests.

^aThis category includes the following CDER divisions: Pulmonary, Allergy, and Rheumatology; Cardiology and Renal; Transplant and Ophthalmology; Medical Imaging; Metabolism and Endocrine; Dermatology and Dental; Anesthesia, Analgesia, and Addiction; Psychiatry; and Bone, Reproductive, and Urology.

Similarly, for requests reviewed by CBER, one of its three offices—the Office of Tissues and Advanced Therapies—reviewed 484 of the 692 total requests, which accounted for approximately 70 percent of the requests reviewed by that center.²⁷ (See table 3.)

Table 3: Number of Expanded Access Requests Reviewed by Food and Drug Administration’s (FDA) Center for Biologics Evaluation and Research (CBER), by Office and Type of Request, Fiscal Years 2012 through 2015

Office	Single-patient		Multiple patients		Total	Percent
	Emergency	Non-emergency	Intermediate-size	Treatment (widespread)		
Tissues and Advanced Therapies ^a	142	320	14	8	484	69.9
Vaccine Research and Review	96	4	14	0	114	16.5
Blood Research and Review	91	0	2	1	94	13.6
Total	329	324	30	9	692	100.0

Source: GAO analysis of FDA data. | GAO-17-564

Note: This table includes both expanded access IND requests and expanded access protocol requests.

^aAccording to FDA, advanced therapies include cellular products, therapeutic vaccines, and gene therapies.

FDA Typically Responded to Emergency Expanded Access Requests in Less than 1 Day and Responded to All Other Requests within the Allotted 30-day Time Frame

FDA officials told us that it only tracks response times for expanded access IND requests (not protocol requests), and, from fiscal years 2012 through 2015, the agency typically responded to emergency expanded access IND requests in less than 1 day, according to FDA data. These data also show that the agency responded to all other expanded access IND requests within the 30 days allotted to the agency, as established in regulation.²⁸ FDA officials reported that, given the nature of emergency expanded access IND requests, they try to respond to these requests within hours of receiving them. From fiscal years 2012 through 2015, of the more than 2,300 emergency expanded access IND requests that

²⁷According to FDA, advanced therapies include cellular products, therapeutic vaccines, and gene therapies.

²⁸See 21 C.F.R. § 312.305(d) (2016).

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were submitted, FDA's median response time was within less than a day.
(See table 4.)

Table 4: Median Food and Drug Administration (FDA) Review Time Frames, in Days, for Expanded Access IND Requests by Center, Type, and Whether the Request Was Allowed to Proceed, Fiscal Years 2012 through 2015

FDA center	Single-Patient						Multiple Patients					
	Emergency			Non-emergency			Intermediate-size			Treatment (widespread)		
	Allowed to proceed											
	No.	Median	Max	No.	Median	Max	No.	Median	Max	No.	Median	Max
Center for Drug Evaluation and Research	2,094	<1	15	2,483	3.0	30	136	30.0	30	0	N/A	N/A
Center for Biologics Evaluation and Research	257	<1	25	118	19.0	30	11	30.0	30	5	30.0	30

FDA center	Single-Patient						Multiple Patients					
	Emergency			Non-emergency			Intermediate-size			Treatment (widespread)		
	Not allowed to proceed											
	No.	Median	Max	No.	Median	Max	No.	Median	Max	No.	Median	Max
Center for Drug Evaluation and Research	10	<1	4	8	25.5	30	4	27.0	28	0	N/A	N/A
Center for Biologics Evaluation and Research	4	<1	<1	20	28.0	30	3	15.0	30	0	N/A	N/A

Legend: N/A = not applicable
 Source: GAO analysis of FDA data. | GAO-17-564.

Note: This table only includes data on expanded access IND requests. It does not include expanded access protocol requests because data were unavailable.

For non-emergency single-patient IND requests that were allowed to proceed, the median number of days to review the requests among the two centers ranged from 3 days to 19 days, and was 30 days for both intermediate-size and treatment requests. Under FDA’s rules, unless a request is not allowed to proceed, an expanded access IND request goes into effect 30 days after FDA receives it or on earlier notification by FDA that the expanded access use may begin.²⁹

²⁹See 21 C.F.R. § 312.305(d) (2016).

FDA officials told us that the agency does not track the time it takes to respond to expanded access protocol requests for various reasons. First, because there are so few protocol requests compared to expanded access IND requests, FDA officials said that the data on time frames for protocols are less meaningful. Second, because expanded access protocol requests are associated with existing INDs that have previously approved treatment plans, all expanded access protocol requests are allowed to proceed as soon as FDA receives the request, except for the treatment category of expanded access protocol requests (i.e., for large sized or widespread patient groups). FDA imposes a 30-day review period on expanded access treatment protocol requests due to the potential for exposing large groups of patients to an investigational drug. If FDA has not otherwise responded to an expanded access treatment protocol request within 30 days, the request is automatically allowed to proceed.

Selected Manufacturers and FDA Consider a Number of Factors in Reviewing Expanded Access Requests

The nine selected manufacturers from whom we obtained information reported that they consider a wide range of factors when reviewing expanded access requests. The factors ranged from those related to the specific patients who would receive a drug to how expanded access might affect the drug development process. Specific factors that were commonly reported as used in reviews by the manufacturers we spoke with included patient factors and drug development factors.

Patient factors that were commonly reported included the following:

- **The patient's condition and treatment history.** For example, one manufacturer told us that the patient must have a disease that is "serious" or "life-threatening" and have no comparable or satisfactory alternative treatment available to the patient.
- **The patient's eligibility for a clinical trial.** For example, one manufacturer said that it assesses whether the patient is ineligible to enroll in a clinical trial for a medically valid reason or meets eligibility criteria for an ongoing trial but seeks treatment in a location without access to that trial.

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- **Whether the potential benefits of treatment outweigh the potential risks to the patient.** For example, one manufacturer reported that providing investigational drugs with limited safety data in an uncontrolled setting could increase the potential for significant adverse events to occur.
 - **The bioethical implications of providing drugs through expanded access.** For example, one manufacturer said that it considers whether providing its drug through expanded access for one patient ethically obligates it to provide its drug to all patients who request it.

Drug development factors that were commonly reported included the following:

- **Reducing participation in clinical trials by approving expanded access requests.** For example, one manufacturer said that as patients become increasingly aware of the availability of an investigational drug through expanded access, manufacturers may face challenges enrolling a sufficient number of patients for clinical trial studies because patients receiving the drug through expanded access are guaranteed the investigational drug (as opposed to participants in a clinical trial who can have a chance of receiving a placebo).
- **The risk that adverse events experienced by patients using an unapproved drug through the expanded access program could compromise the drug development process.** For example, some manufacturers raised concerns that, because an investigational drug is administered in an uncontrolled setting under expanded access, any data reported from such adverse events could complicate the safety findings for that drug during FDA's review of those data and contribute to a decision to not approve the drug.
- **The potential public backlash that could arise against the manufacturer should an expanded access request be denied.** For example, one manufacturer told us that denying an expanded access request could lead to negative publicity through social media. This negative publicity could, in turn, deter potential investors from funding the drug's development.
- **The requested drug's availability.** For example, one manufacturer said that it evaluates whether it has enough supply of its drug available to successfully administer its clinical trial, as well as to provide the drug to expanded access patients. Another manufacturer said that this is a particular concern early in the drug development process, as manufacturers typically only produce the amount of drug needed to support each clinical trial phase. Generally, the drug's supply is low in the early clinical phases and increases in the later clinical phases.
- **The financial and administrative resources required to fulfill the request.** Manufacturers said that resource requirements could particularly impact smaller manufacturers that have fewer resources available to process expanded access requests and administer clinical trials simultaneously.

FDA officials told us that the factors they consider when reviewing expanded access requests to determine whether that request should be allowed to proceed are based on criteria in regulation.³⁰ Specifically, upon receipt of an expanded access request, FDA officials said that they review that request against the following four general criteria established in regulation:

1. The patient has a serious or immediately life-threatening disease or condition.
2. There is no comparable or satisfactory alternative therapy.
3. The potential benefit justifies the potential risks of the treatment, and those potential risks are not unreasonable in the context of the disease or condition to be treated.
4. Providing the drug will not interfere with clinical investigations that could support marketing approval of the drug or otherwise compromise development of the expanded access use for that drug.

In addition to these general criteria applicable to all expanded access requests, FDA officials reported that they consider additional criteria in regulation that apply to specific types of expanded access.

- **Single-patient requests:** The physician must determine that the probable risk to the patient from the investigational drug is not greater than the probable risk from the disease or condition and FDA must determine that the patient cannot obtain the drug under another IND or protocol.³¹
- **Intermediate-size populations:** FDA must determine that there is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial of the drug in the approximate number of patients expected to receive it under expanded access. In addition, there must be preliminary clinical evidence of effectiveness of the drug or a plausible pharmacological effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.³²

³⁰See 21 C.F.R. 312.305(a) (2016) (establishing criteria for all expanded access uses).

³¹See 21 C.F.R. 312.310(a) (2016) (establishing criteria for individual patients).

³²See 21 C.F.R. 312.315(b) (2016) (establishing criteria for intermediate-size patient populations).

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- **Treatment INDs or protocols:** FDA must determine that the drug is being investigated in a controlled clinical trial (or that all clinical trials of the drug have been completed) and that the IND sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence. Additionally, when expanded access use is for a serious disease or condition, FDA must determine that there is sufficient clinical evidence of safety and effectiveness to support the expanded access use. When expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, must provide a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury.³³

FDA officials told us that, in addition to these criteria, agency reviewers will also consider whether submitted requests have provided sufficient information to allow FDA to make an informed decision on the request.

³³See 21 C.F.R. 312.320(a) (2016) (establishing criteria for treatment INDs or protocols).

FDA and Others Have Taken Steps to Improve the Expanded Access Program and Patient Access to Investigational Drugs, but Stakeholders Continue to Cite Concerns

FDA Continues to Undertake Efforts to Improve the Expanded Access Program

According to FDA officials and stakeholders, FDA has undertaken efforts to improve the expanded access program. These efforts include publishing a simplified application form, finalizing existing guidance and making changes to its website for single-patient expanded access IND requests, and working with the Reagan-Udall Foundation—a non-profit established by Congress to assist FDA—to develop a website to help patients and physicians navigate the expanded access process.³⁴

Simplified Application Form, Guidance, and Website

In response to concerns raised by patients and physicians that the process for physicians trying to request expanded access to drugs for single patients was complex and cumbersome, FDA issued a new simplified, alternative application form for these requests (Form FDA 3926) in June 2016, finalized its related guidance, and made changes to its website. According to FDA, prior to these changes physicians who wanted expanded access for a single patient had to complete and submit the same form that manufacturers complete when establishing clinical trials (Form FDA 1571). According to FDA officials, the new form requires the physician to complete 11 elements of information, far fewer than the 26 elements identified on Form FDA 1571. FDA officials estimate that the new application will take physicians, on average, 45 minutes to complete.

In addition to the new application, FDA finalized another guidance document which provided more details on the implementation of FDA expanded access regulations, to further assist physicians in the expanded

³⁴See 21 U.S.C. § 379dd (establishment and functions of Reagan-Udall Foundation).

access process.³⁵ FDA has also redesigned its expanded access website pages to explain the new form and guidance document in detail.

Most stakeholders, including physicians, spoke positively about the new application and some said the new application is easier and takes less time to complete compared to Form FDA 1571. However, even with these changes, a few of the stakeholders that we spoke with said the revised website and forms may still be hard to understand, particularly for physicians and patients who have no prior experience with expanded access requests.

Website to Help Physicians and Patients

In response to concerns from patients and patient advocates that it is difficult to locate and understand information about single-patient expanded access IND requests, FDA asked the Reagan-Udall Foundation to develop a website—referred to as the Expanded Access Navigator—that will help physicians and patients find relevant information about the process.³⁶ According to the foundation's proposal, the Navigator will include a directory of manufacturers' expanded access policies, procedures, and points of contact. The Navigator will also offer information on IRBs and reporting requirements for physicians. Foundation officials also told us that FDA has been helping with this effort by identifying issues and reviewing the content of the Navigator, and that the website is expected to launch in June 2017.

Foundation officials noted that key challenges with the website include determining how to keep its information current and how to get potentially cautious manufacturers to provide the needed information. Some stakeholders told us they were skeptical the website could be maintained with updated information or were concerned that it could be a duplication of the information found on ClinicalTrials.gov.³⁷ However, the proposal for the Navigator website states that it would not duplicate the information on ClinicalTrials.gov. Other stakeholders told us that the Navigator could

³⁵FDA, *Expanded Access to Investigational Drugs for Treatment Use— Questions and Answers: Guidance for Industry* (Silver Spring, Md.:June 2016).

³⁶The Reagan-Udall Foundation is a nonprofit organization created by Congress to advance the mission of FDA for the purpose of advancing regulatory science.

³⁷The website ClinicalTrials.gov is a web-based resource for patients and physicians to access information about clinical trials.

help patients quickly and efficiently obtain information on drug manufacturers' expanded access policies and information. This type of website appears to complement a provision in the recently enacted 21st Century Cures Act, which requires manufacturers to make their expanded access policies publically available.

Other Stakeholders Are Working to Improve the Expanded Access Process and Increase Patient Access to Drugs

Some stakeholder groups are taking steps to improve the expanded access process through efforts to streamline the IRB process, help manufacturers manage expanded access requests for drugs, and increase patient access through legislative changes.

Streamlining the IRB Process

In response to concerns raised by stakeholders, including manufacturers and patient advocacy groups, that IRB involvement in the expanded access process increases the time it takes for patients to obtain access to drugs in single-patient IND situations and that IRBs lack a full understanding of the expanded access program, the WCG Foundation is developing a project to streamline the IRB process and educate IRBs.³⁸ According to the foundation officials, the timeliness of IRB reviews is hindered by the IRB's unfamiliarity with the expanded access review process, which may occur only once every few years for some IRBs. In addition, foundation officials said that even though FDA has developed the abbreviated Form FDA 3926 for physicians to use for single-patient expanded access IND requests, some IRBs continue to require the use of the longer form (Form FDA 1571) as the basis for their review of the application, which could slow the process further. See appendix I for a copy of Form FDA 1571 and appendix II for a copy of Form FDA 3926.

The foundation's project aims to overcome these obstacles by working with IRBs to meet and respond to a physician single-patient IND request within 72 hours from the date the request was received. In addition, they must agree to adopt FDA's simplified application (Form FDA 3926) for

³⁸The WCG Foundation is a non-profit organization, founded by the WIRB-Copernicus Group, whose mission is to help improve protections for research participants and improve the health and well-being for all people.

single-patient IND requests. Some of the intended outcomes for the project include establishing a core group of IRBs with expanded access experience, streamlining the IRB process by providing the IRB community with a standard form for reviewing expanded access requests, and educating the broader national IRB community on using a streamlined IRB process. FDA officials said the agency supports WCG's efforts and is meeting with foundation officials on a regular basis. Some of the stakeholders that we spoke with noted that more education and guidance for IRBs on how to handle expanded access requests is needed.

Pilot to Help Drug Manufacturers Manage Expanded Access Requests

To address concerns that drug manufacturers' decisions on expanded access requests could be biased or unfair, the drug manufacturer Janssen Pharmaceuticals Companies of Johnson & Johnson is piloting a process through which it receives recommendations about which patients should receive expanded access from a third party group.³⁹ Specifically, in May 2015, Johnson & Johnson announced a partnership between Janssen and the Compassionate Use Advisory Committee (CompAC) at the New York University (NYU) School of Medicine's Division of Medical Ethics. At the time the committee was established, Janssen was receiving numerous expanded access requests for a drug it was developing to treat a form of cancer, but the drug had not yet been approved for marketing by FDA. According to officials from Janssen and NYU CompAC, Janssen decided it needed help with allocating the drug fairly and transparently to patients outside of clinical trials. The committee, which consists of medical experts, bioethicists, and patient representatives, meets weekly to review anonymized expanded access requests submitted to Janssen, evaluate each request against a set of criteria the committee developed, and provide Janssen with a suggested approach for each request. Between July 1 and December 31, 2015, the committee recommended that Janssen approve 60 of 76 requests that it reviewed. Janssen reported that it approved all 60 of these requests recommended by the committee, and, based on the positive experience with the pilot, the manufacturer is planning to expand the program to additional investigational drugs.

³⁹Janssen is an arm of Johnson & Johnson.

Efforts to Increase Access to Drugs through State Legislative Changes

In an effort to help facilitate patient access to investigational drugs, the Goldwater Institute—a public policy research organization—developed model legislation for states.⁴⁰ The institute’s model legislation, which is referred to as Right-to-Try, would place limitations under state law on liability lawsuits and licensing actions against individuals or entities involved in the care of individuals seeking expanded access. The institute officials stated that such legislation would provide incentives for manufacturers and physicians to provide access to such drugs. According to the institute’s officials, the model legislation applies only to drugs that have successfully completed phase I clinical safety trials. According to the Goldwater Institute, as of June 2017, 37 states had enacted Right-to-Try laws similar to this model.

The stakeholders we spoke with, including representatives of drug manufacturers and patient and physician advocacy groups, reported concerns about these legislative changes:

- Some contended that the laws would not help patients gain access to investigational drugs because they do not compel manufacturers to give access. As we previously noted, manufacturers have cited various reasons why they may not give a patient access to their investigational drug, and it is unclear to what extent these laws would address these concerns.
- Others raised concerns that the laws might give patients false hope that experimental drugs will cure them. Thus, patients may not fully consider the risks associated with these drugs, which may not be effective and which could potentially be more harmful than no treatment.

⁴⁰The Goldwater Institute, which was established in 1988, is an independent, non-partisan public policy research organization that focuses on developing state policy solutions to protect people’s rights.

FDA Reported Limited Use of Expanded Access Safety Data in its Drug Approval Process, and Some Manufacturers Have Asked for More Clarity on This Use by FDA

FDA reported using expanded access safety data, specifically adverse events data, in a few cases in approving new drugs for marketing in the United States and not more widely because expanded use situations generally lack controls used in most clinical trials.⁴¹ FDA guidance specifies that safety data, which include any unexpected adverse events that are associated with the use of a drug, even during expanded access use, must be reported along with safety data from clinical trials. Agency officials noted that these data can contribute important safety information that might not otherwise be collected in clinical trials and that they take into account the context of the expanded access situation, such as use in patients with serious or life-threatening ailments, when reviewing new drug applications (NDA) and biologics license applications (BLA). For example, officials said that in some cases adverse events data from expanded access use can identify rare side effects not detected in clinical trials, as well as inform FDA reviewers of any safety issues involving patient populations that were not otherwise included in the drug's clinical trials. FDA's primary goal of the expanded access program is to allow patients with no other options access to investigational drugs when appropriate. Data from expanded access use can also help FDA meet its agency goal of collecting meaningful data about the use of investigational drugs.⁴²

⁴¹Sponsors of INDs and all cases of expanded access are responsible for submitting safety reports to FDA that include adverse events data resulting from clinical trials to be used in assessing the safety of a drug within the drug approval process. See 21 C.F.R. §§ 312.32, 312.305(c)(5) (2016).

⁴²According to FDA officials, data from expanded access use can also provide insights on a drug's effectiveness in limited situations. In addition, some of the nine manufacturers we spoke with reported using safety and efficacy data from expanded access situations to help them evaluate their drug. For example, officials from one manufacturer reported that a benefit of implementing an expanded access protocol over an IND is that the manufacturer can collect additional information on the drug's efficacy and safety. Officials from another manufacturer also told us they use data from expanded access use to make changes to the drug's palatability or dosage before the drug is approved by FDA.

However, several stakeholders we spoke with, including the selected manufacturers, raised concerns that FDA is not clear about how it uses expanded access adverse events data in its review of NDAs and BLAs. Some of the manufacturers noted that use of such data may influence FDA in making final approval decisions and that this possibility can contribute to a manufacturer deciding not to grant patients access to their drug through the expanded access program. Some of the manufacturers reported that they have concerns about the possibility that FDA's use of adverse events data from expanded access requests would result in a clinical hold on their drug, which would halt all testing on human subjects and, as a result, delay the drug's development process. One study included a review of ten years (2005 through 2014) of expanded access data to determine how often a clinical hold was put on a drug that was obtained via expanded access.⁴³ This review only found two instances in which adverse events from expanded access use contributed to a decision to have a clinical hold put on a drug. However, manufacturers continued to raise concerns about how FDA uses adverse events data from expanded access use.

FDA briefly mentions its perspective on how adverse events data from expanded access are viewed in NDAs and BLAs; but, the information is vague and is not consistently communicated in other documents FDA uses to communicate with manufacturers on expanded access use. Specifically, our review of FDA's regulations and nine related documents FDA uses to communicate with manufacturers regarding expanded access use found little information communicating how FDA uses adverse events data from expanded access in new drug application reviews. Our review included FDA's three new guidance documents on expanded access, four letters of acknowledgement FDA sends to sponsors after they submit an expanded access request, and two guidance documents on IND safety reporting (a 2012 final document and 2015 draft of new

⁴³Jonathan P. Jarow, Steven Lemery, Kevin Bugin, Sean Khozin, and Richard Moscicki, "Expanded Access of Investigational Drugs: The Experience of Drug Evaluation and Research Over a 10-Year Period," *Therapeutic Innovation & Regulatory Science*, vol. 50, no.6 (2016).

guidance).⁴⁴ Only one of the documents—its expanded access treatment use guidance that was issued in June of 2016—refers to how expanded access data might be used by FDA in the drug approval process. According to FDA officials, it included this reference in response to manufacturer’s requests that more clarity be provided on how these data would be used. Although FDA took steps to improve its communication on this, the information in the document is vague in that it contains few details and no specific examples. The specific language is as follows:

“...There are a small number of cases in which FDA has used adverse event information from expanded access in the safety assessment of a drug. However, FDA reviewers of these adverse event data understand the context in which the expanded access use was permitted (e.g., use in patients with serious or immediately life-threatening diseases or administered in a clinical setting (not clinical trial)) and will evaluate any adverse event data obtained from an expanded access submission within that context....”⁴⁵

According to standards for internal control in the federal government, management should ensure adequate means of communicating with external stakeholders who have a significant impact on the agency achieving its goal.⁴⁶ While FDA officials told us that they believe manufacturers are aware of how the agency uses adverse events data from expanded access use, some of the manufacturers and other stakeholders told us they did not think the guidance was clear. Some manufacturers also noted that the lack of clear information about how FDA uses these data can influence their decision not to give patients access to their drugs. This could impact FDA’s goal of facilitating

⁴⁴The three guidance documents on expanded access were FDA, *Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers: Guidance for Industry* (Silver Spring, Md; June 2016); FDA, *Individual Patient Expanded Access Applications: Form FDA 3926 Guidance for Industry* (Silver Spring, Md: June 2016); and FDA, *Charging for Investigational Drugs under an IND—Questions and Answers: Guidance for Industry* (Silver Spring, Md: June 2016). The two guidance documents on IND safety reporting were FDA, *Safety Reporting Requirements for INDs and BA/BE Studies* (Silver Spring, Md: December 2012) and FDA, *Safety Assessment for IND Safety Reporting (Draft)* (Silver Spring, Md: December 2015). We also reviewed FDA regulations pertaining to expanded access use: 21 C.F.R. pt. 312, subpt. I, §§ 312.300 et seq. (2016).

⁴⁵FDA, *Expanded Access to Investigational Drugs*, p. 18.

⁴⁶GAO-14-704G.

expanded access to drugs for treatment use by patients with serious or life-threatening diseases or conditions, when appropriate.

Conclusions

FDA's expanded access program was established to facilitate access, when appropriate, to investigational drugs for certain patients when no other comparable medical options are available. Although FDA provides clear guidance on the expanded access data that must be submitted by physicians and manufacturers and recently took steps to communicate how it will use these data, the agency's communication lacks clarity and specificity. In addition, this information is not consistently communicated in other documents that FDA uses to communicate with manufacturers about the program. Manufacturers and other stakeholders expressed concerns about this lack of clarity, and some noted that, without a better understanding of the how the data will be used, they may be more likely to deny expanded access requests for fear that any adverse events associated with these often terminally ill patients may delay the development of the drug should FDA place a clinical hold due to the adverse event. Such delays in clinical trials can have a significant impact on a manufacturer, especially on small companies trying to make a drug available to a larger patient population. Without clearly communicated information from FDA on how adverse event data from expanded access is used, manufacturers do not have the information they need to make informed decisions about expanded access.

Recommendation for Executive Action

To help FDA meet its goal of facilitating expanded access to investigational drugs by patients with serious or life-threatening diseases or conditions, when appropriate, the Commissioner of FDA should clearly communicate how the agency will use adverse event data from expanded access use when reviewing drugs and biologics for approval for marketing and sale in the United States.

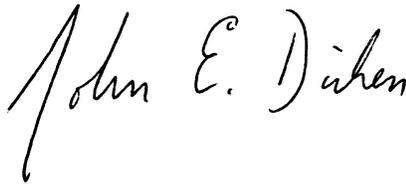
Agency Comments

We provided a draft of this report to HHS for comment. In its comments, reproduced in appendix III, HHS concurred with our recommendation. HHS noted that while there have only been two instances in which

adverse event data have contributed to decisions to temporarily put development of investigational drugs on partial clinical holds, additional clarity on how FDA uses such data from expanded access use may allay manufacturers concerns. HHS also provided technical comments, which we incorporated as appropriate.

We are sending copies of this report to the congressional addressees, the Secretary of Health & 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 staffs have any questions about this report, please contact me at (202) 512-7114 or dickenj@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix IV.

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

John E. Dicken
Director, Health Care

List of Addressees

The Honorable John Hoeven
Chairman
The Honorable Jeff Merkley
Ranking Member
Subcommittee on Agriculture, Rural Development, Food and Drug
Administration, and Related Agencies
Committee on Appropriations
United States Senate

The Honorable Robert Aderholt
Chairman
The Honorable Sanford Bishop
Ranking Member
Subcommittee on Agriculture, Rural Development, Food and Drug
Administration, and Related Agencies
Committee on Appropriations
House of Representatives

The Honorable Tom Carper
United States Senate

The Honorable Ron Johnson
United States Senate

The Honorable Michael McCaul
House of Representatives

The Honorable Fred Upton
House of Representatives

Appendix I: Form FDA 1571, Investigational New Drug Application

Food and Drug Administration's (FDA) Form FDA 1571 contains a number of administrative elements pertaining to an investigational new drug application. This form is completed and submitted to FDA by manufacturers who seek FDA's approval to conduct clinical trials of an investigational drug on humans.

**Appendix I: Form FDA 1571, Investigational
New Drug Application**

<input type="button" value="Next Page"/> <input type="button" value="Export Data"/> <input type="button" value="Import Data"/> <input type="button" value="Reset Form"/>		
DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration INVESTIGATIONAL NEW DRUG APPLICATION (IND) <i>(Title 21, Code of Federal Regulations (CFR) Part 312)</i>		Form Approved: OMB No. 0910-0014 Expiration Date: February 28, 2019 See <i>PRA Statement on page 3.</i> NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)
1. Name of Sponsor		2. Date of Submission (mm/dd/yyyy)
3. Sponsor Address		4. Telephone Number (Include country code if applicable and area code)
Address 1 (Street address, P.O. box, company name c/o)		
Address 2 (Apartment, suite, unit, building, floor, etc.)		
City	State/Province/Region	
Country	ZIP or Postal Code	
5. Name(s) of Drug (Include all available names: Trade, Generic, Chemical, or Code)		6. IND Number (if previously assigned)
		<input type="button" value="Continuation Page for #5"/>
7. (Proposed) Indication for Use		Is this indication for a rare disease (prevalence <200,000 in U.S.)? <input type="checkbox"/> Yes <input type="checkbox"/> No Does this product have an FDA Orphan Designation for this indication? <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, provide the Orphan Designation number for this indication: <input type="text"/>
		<input type="button" value="Continuation Page for #7"/>
8. Phase(s) of Clinical Investigation to be conducted <input type="checkbox"/> Phase 1 <input type="checkbox"/> Phase 2 <input type="checkbox"/> Phase 3 <input type="checkbox"/> Other (Specify): _____		
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314), Drug Master Files (21 CFR Part 314.420), and Biologics License Applications (21 CFR Part 601) referred to in this application.		
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.		Serial Number _____
11. This submission contains the following (Select all that apply)		
<input type="checkbox"/> Initial Investigational New Drug Application (IND) <input type="checkbox"/> Response to Clinical Hold <input type="checkbox"/> Response To FDA Request For Information <input type="checkbox"/> Request For Reactivation Or Reinstatement <input type="checkbox"/> Annual Report <input type="checkbox"/> General Correspondence <input type="checkbox"/> Development Safety Update Report (DSUR) <input type="checkbox"/> Other (Specify): _____		
Protocol Amendment(s) <input type="checkbox"/> New Protocol <input type="checkbox"/> Change in Protocol <input type="checkbox"/> New Investigator <input type="checkbox"/> PMR/PMC Protocol	Information Amendment(s) <input type="checkbox"/> Chemistry/Microbiology <input type="checkbox"/> Pharmacology/Toxicology <input type="checkbox"/> Clinical <input type="checkbox"/> Statistics <input type="checkbox"/> Clinical Pharmacology	Request for <input type="checkbox"/> Meeting <input type="checkbox"/> Proprietary Name Review <input type="checkbox"/> Special Protocol Assessment <input type="checkbox"/> Formal Dispute Resolution
IND Safety Report(s) <input type="checkbox"/> Initial Written Report <input type="checkbox"/> Follow-up to a Written Report		
12. Select the following only if applicable. (Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)		
<i>Expanded Access Use, 21 CFR 312.300</i>		
<input type="checkbox"/> Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f) <input type="checkbox"/> Charge Request, 21 CFR 312.8	<input type="checkbox"/> Individual Patient, Non-Emergency 21 CFR 312.310 <input type="checkbox"/> Individual Patient, Emergency 21 CFR 312.310(d)	<input type="checkbox"/> Intermediate Size Patient Population, 21 CFR 312.315 <input type="checkbox"/> Treatment IND or Protocol, 21 CFR 312.320
For FDA Use Only		
CBER/DCC Receipt Stamp	DDR Receipt Stamp	Division Assignment
		IND Number Assigned

**Appendix I: Form FDA 1571, Investigational
New Drug Application**

Previous Page	Next Page		
<p>13. Contents of Application – This application contains the following items <i>(Select all that apply)</i></p> <table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top;"> <input type="checkbox"/> 1. Form FDA 1571 (21 CFR 312.23(a)(1)) <input type="checkbox"/> 2. Table of Contents (21 CFR 312.23(a)(2)) <input type="checkbox"/> 3. Introductory statement (21 CFR 312.23(a)(3)) <input type="checkbox"/> 4. General Investigational plan (21 CFR 312.23(a)(3)) <input type="checkbox"/> 5. Investigator's brochure (21 CFR 312.23(a)(5)) <input type="checkbox"/> 6. Protocol(s) (21 CFR 312.23(a)(6)) <ul style="list-style-type: none"> <input type="checkbox"/> a. Study protocol(s) (21 CFR 312.23(a)(6)) <input type="checkbox"/> b. Investigator data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572 <input type="checkbox"/> c. Facilities data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572 </td> <td style="width: 50%; vertical-align: top;"> 6. Protocol(s) (Continued) <ul style="list-style-type: none"> <input type="checkbox"/> d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572 <input type="checkbox"/> 7. Chemistry, manufacturing, and control data (21 CFR 312.23(a)(7)) <ul style="list-style-type: none"> <input type="checkbox"/> Environmental assessment or claim for exclusion (21 CFR 312.23(a)(7)(iv)(e)) <input type="checkbox"/> 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8)) <input type="checkbox"/> 9. Previous human experience (21 CFR 312.23(a)(9)) <input type="checkbox"/> 10. Additional information (21 CFR 312.23(a)(10)) <input type="checkbox"/> 11. Biosimilar User Fee Cover Sheet (Form FDA 3792) <input type="checkbox"/> 12. Clinical Trials Certification of Compliance (Form FDA 3674) </td> </tr> </table>		<input type="checkbox"/> 1. Form FDA 1571 (21 CFR 312.23(a)(1)) <input type="checkbox"/> 2. Table of Contents (21 CFR 312.23(a)(2)) <input type="checkbox"/> 3. Introductory statement (21 CFR 312.23(a)(3)) <input type="checkbox"/> 4. General Investigational plan (21 CFR 312.23(a)(3)) <input type="checkbox"/> 5. Investigator's brochure (21 CFR 312.23(a)(5)) <input type="checkbox"/> 6. Protocol(s) (21 CFR 312.23(a)(6)) <ul style="list-style-type: none"> <input type="checkbox"/> a. Study protocol(s) (21 CFR 312.23(a)(6)) <input type="checkbox"/> b. Investigator data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572 <input type="checkbox"/> c. Facilities data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572 	6. Protocol(s) (Continued) <ul style="list-style-type: none"> <input type="checkbox"/> d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572 <input type="checkbox"/> 7. Chemistry, manufacturing, and control data (21 CFR 312.23(a)(7)) <ul style="list-style-type: none"> <input type="checkbox"/> Environmental assessment or claim for exclusion (21 CFR 312.23(a)(7)(iv)(e)) <input type="checkbox"/> 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8)) <input type="checkbox"/> 9. Previous human experience (21 CFR 312.23(a)(9)) <input type="checkbox"/> 10. Additional information (21 CFR 312.23(a)(10)) <input type="checkbox"/> 11. Biosimilar User Fee Cover Sheet (Form FDA 3792) <input type="checkbox"/> 12. Clinical Trials Certification of Compliance (Form FDA 3674)
<input type="checkbox"/> 1. Form FDA 1571 (21 CFR 312.23(a)(1)) <input type="checkbox"/> 2. Table of Contents (21 CFR 312.23(a)(2)) <input type="checkbox"/> 3. Introductory statement (21 CFR 312.23(a)(3)) <input type="checkbox"/> 4. General Investigational plan (21 CFR 312.23(a)(3)) <input type="checkbox"/> 5. Investigator's brochure (21 CFR 312.23(a)(5)) <input type="checkbox"/> 6. Protocol(s) (21 CFR 312.23(a)(6)) <ul style="list-style-type: none"> <input type="checkbox"/> a. Study protocol(s) (21 CFR 312.23(a)(6)) <input type="checkbox"/> b. Investigator data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572 <input type="checkbox"/> c. Facilities data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572 	6. Protocol(s) (Continued) <ul style="list-style-type: none"> <input type="checkbox"/> d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572 <input type="checkbox"/> 7. Chemistry, manufacturing, and control data (21 CFR 312.23(a)(7)) <ul style="list-style-type: none"> <input type="checkbox"/> Environmental assessment or claim for exclusion (21 CFR 312.23(a)(7)(iv)(e)) <input type="checkbox"/> 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8)) <input type="checkbox"/> 9. Previous human experience (21 CFR 312.23(a)(9)) <input type="checkbox"/> 10. Additional information (21 CFR 312.23(a)(10)) <input type="checkbox"/> 11. Biosimilar User Fee Cover Sheet (Form FDA 3792) <input type="checkbox"/> 12. Clinical Trials Certification of Compliance (Form FDA 3674)		
<p>14. Is any part of the clinical study to be conducted by a contract research organization? <input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, will any sponsor obligations be transferred to the contract research organization? <input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred <i>(use continuation page)</i>.</p>			
Continuation Page for #14			
15. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations			
16. Name(s) and Title(s) of the person(s) responsible for review and evaluation of information relevant to the safety of the drug			
<p>I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold or financial hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.</p>			
17. Name of Sponsor or Sponsor's Authorized Representative			
18. Telephone Number <i>(Include country code if applicable and area code)</i>	19. Facsimile (FAX) Number <i>(Include country code if applicable and area code)</i>		
20. Address			
Address 1 <i>(Street address, P.O. box, company name c/o)</i>			
Address 2 <i>(Apartment, suite, unit, building, floor, etc.)</i>			
City	State/Province/Region		
Country	ZIP or Postal Code		
21. Email Address			
22. Date of Sponsor's Signature <i>(mm/dd/yyyy)</i>			
23. Name of Countersigner			
24. Address of Countersigner			
Address 1 <i>(Street address, P.O. box, company name c/o)</i>			
Address 2 <i>(Apartment, suite, unit, building, floor, etc.)</i>			
City	State/Province/Region		
Country	ZIP or Postal Code		
United States of America			
WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).			
25. Signature of Sponsor or Sponsor's Authorized Representative	26. Signature of Countersigner		
Sign	Sign		

**Appendix I: Form FDA 1571, Investigational
New Drug Application**

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

The burden time for this collection of information is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Please do NOT send your completed form to this PRA Staff email address.

Appendix II: Form FDA 3926, Individual Patient Expanded Access Investigational New Drug Application

Food and Drug Administration's (FDA) Individual Patient Expanded Access Application, Form FDA 3926, is to be completed and submitted to FDA by a patient's physician requesting single-patient expanded access of an investigational drug.

Appendix II: Form FDA 3926, Individual Patient Expanded Access Investigational New Drug Application

DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration Individual Patient Expanded Access Investigational New Drug Application (IND) <i>(Title 21, Code of Federal Regulations (CFR) Part 312)</i>		Form Approved: OMB No. 0910-0814 Expiration Date: April 30, 2019 See PRA Statement on last page.
1. Patient's Initials		2. Date of Submission (mm/dd/yyyy)
3.a. Initial Submission <input type="checkbox"/> Select this box if this form is an initial submission for an individual patient expanded access IND, and complete only fields 4 through 8, and fields 10 and 11.	3.b. Follow-Up Submission <input type="checkbox"/> Select this box if this form accompanies a follow-up submission to an existing individual patient expanded access IND, and complete the items to the right in this section, and fields 8 through 11.	Investigational Drug Name Physician's IND Number
4. Clinical Information		
Indication		
Brief Clinical History <i>(Patient's age, gender, weight, allergies, diagnosis, prior therapy, response to prior therapy, reason for request, including an explanation of why the patient lacks other therapeutic options)</i>		
5. Treatment Information		
Investigational Drug Name		
Name of the entity that will supply the drug <i>(generally the manufacturer)</i>		
FDA Review Division <i>(if known)</i>		
Treatment Plan <i>(Including the dose, route and schedule of administration, planned duration, and monitoring procedures. Also include modifications to the treatment plan in the event of toxicity.)</i>		
6. Letter of Authorization (LOA), if applicable <i>(generally obtained from the manufacturer of the drug)</i>		
<input type="checkbox"/> I have attached the LOA. <i>(Attach the LOA; if electronic, use normal PDF functions for file attachments.)</i>		
Note: If there is no LOA, consult the Form Instructions.		
7. Physician's Qualification Statement <i>(Including medical school attended, year of graduation, medical specialty, state medical license number, current employment, and job title. Alternatively, attach the first few pages of physician's curriculum vitae (CV), provided they contain this information. If attaching the CV electronically, use normal PDF functions for file attachments.)</i>		
8. Physician Name, Address, and Contact Information		
Physician Name <i>(Sponsor)</i>	Email Address of Physician	
Address 1 <i>(Street address, No P.O. boxes)</i>		
Address 2 <i>(Apartment, suite, unit, building, floor, etc.)</i>	Telephone Number of Physician	
City	State	Facsimile (FAX) Number of Physician
ZIP Code	Physician's IND number, if known	
FORM FDA 3926 (2/16)		
Page 1 of 2		
PSC Publishing Services (301) 443-6740 EF		

**Appendix II: Form FDA 3926, Individual Patient
Expanded Access Investigational New Drug
Application**

9. Contents of Submission

This submission contains the following materials, which are attached to this form (select all that apply). If none of the following apply to the follow-up communications, use Form FDA 1571 for your submission.

- | | |
|---|--|
| <input type="checkbox"/> Initial Written IND Safety Report | <input type="checkbox"/> Change in Treatment Plan |
| <input type="checkbox"/> Follow-up to a Written IND Safety Report | <input type="checkbox"/> General Correspondence |
| <input type="checkbox"/> Annual Report | <input type="checkbox"/> Response to FDA Request for Information |
| <input type="checkbox"/> Summary of Expanded Access Use (treatment completed) | <input type="checkbox"/> Response to Clinical Hold |

10. Request for Authorization to Use Form FDA 3926

- I request authorization to submit this Form FDA 3926 to comply with FDA's requirements for an individual patient expanded access IND.

11. Certification Statement: I will not begin treatment until 30 days after FDA's receipt of a completed application and all required materials unless I receive earlier notification from FDA that treatment may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I also certify that I will obtain informed consent, consistent with Federal requirements, and that an Institutional Review Board (IRB) that complies with the Federal IRB requirements will be responsible for initial and continuing review and approval of this treatment use. I understand that in the case of an emergency request, treatment may begin without prior IRB approval, provided the IRB is notified of the emergency treatment within 5 working days of treatment. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

WARNING: A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

Signature of Physician

To enable the signature field, please fill out all prior required fields. For a list of required fields which have not yet been filled out, please click here.

Date

For FDA Use Only

Date of FDA Receipt	Is this an emergency individual patient IND? <input type="checkbox"/> Yes <input type="checkbox"/> No	Is this indication for a rare disease (prevalence < 200,000 in the U.S.)? <input type="checkbox"/> Yes <input type="checkbox"/> No
IND Number		

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 45 minutes per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

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

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



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

JUN 14 2017

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

Dear Mr. Dickens:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "*Investigational New Drugs: FDA Has Taken Steps to Improve the Expanded Access Program but Needs to Clarify How Adverse Events Data Are Used*" (GAO-17-564).

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

Sincerely,

A handwritten signature in cursive script that reads "Barbara Pisaro Clark".

Barbara Pisaro Clark
Acting Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: INVESTIGATIONAL NEW DRUGS: FDA HAS TAKEN STEPS TO IMPROVE THE EXPANDED ACCESS PROGRAM BUT NEEDS TO CLARIFY HOW ADVERSE EVENTS DATA ARE USED (GAO-17-564)

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

The Food and Drug Administration (FDA) is committed to increasing awareness of and knowledge about its expanded access process and the procedures for obtaining access to investigational drugs, and appreciates GAO's recognition of its efforts in this area. For over two decades, FDA has had in place a system that strikes a careful balance between helping patients gain access to investigational drugs, on the one hand, and helping to ensure patient safety and preserving the clinical trial development process on the other. As GAO notes, through its expanded access process, from fiscal years 2012-2015, FDA has conducted timely reviews of nearly 5,800 expanded access requests, and allowed nearly all of them (99 percent) to proceed.

FDA also has made numerous improvements to the expanded access process to make it easier to navigate and more accessible to patients, physicians, and other stakeholders. FDA established an expedited telephone process for daytime and after-hours emergency requests for expanded access, and revamped the regulations regarding expanded access to investigational drugs to make the process and responsibilities of physicians more clear and concise. In June 2016, in response to feedback from physicians that completing the expanded access form (Form FDA 1571) was time-consuming, FDA released a simple new form (Form FDA 3926) for individual patient expanded access INDs. As GAO notes in its report, this form is estimated to take 45 minutes to complete and requires much less information than the previous submission process. Along with the new form, FDA released step-by-step instructions on how to complete it. Almost immediately, physicians began to take advantage of the new form. FDA also finalized a Questions and Answers guidance that explains what expanded access is, when and how to request expanded access, and the type of information that should be included in requests. At the same time, FDA released another guidance that explains the regulations regarding when and how patients may be charged for investigational drugs. Simultaneously, FDA revamped its expanded access website and produced Fact Sheets for physicians and patients. In addition to web pages directed specifically toward patients, physicians and industry, FDA has staff available to assist physicians and patients in understanding how to apply for expanded access.

GAO Recommendation

To help FDA meet its goal of facilitating expanded access to investigational drugs by patients with serious or life-threatening diseases or conditions when appropriate, the Commissioner of FDA should clearly communicate how the agency will use adverse event data from expanded access use when reviewing drugs and biologics for approval for marketing and sale in the United States.

HHS Response

HHS understands that the review of adverse event reports that result from expanded access use must be interpreted with caution, and the Agency is gratified that GAO has recognized that such data help FDA collect meaningful information about the use of investigational drugs. Indeed, Question 25 of FDA's Questions and Answers guidance on expanded access seeks to clarify how the Agency interprets adverse events that arise during expanded access. As GAO notes, citing

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: INVESTIGATIONAL NEW DRUGS: FDA HAS TAKEN STEPS TO IMPROVE THE EXPANDED ACCESS PROGRAM BUT NEEDS TO CLARIFY HOW ADVERSE EVENTS DATA ARE USED (GAO-17-564)

FDA data, there have been only two instances in which adverse events from expanded access use contributed to a decision to put development of an investigational drug on a partial clinical hold. In both instances, the development of the drugs continued after issues were addressed and the holds were lifted. While these data do not support the assertions of some manufacturers that such data may influence FDA in making final approval decisions, FDA nevertheless concurs with GAO's recommendation, recognizing that additional clarity on how the Agency uses adverse event data from expanded access use may help to allay these concerns.

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, Gerardine Brennan, Assistant Director; Carolyn Garvey, Analyst-in-Charge; Nick Bartine; George Bogart; Laurie Pachter; Vikki Porter; and Dharani Ranganathan made key contributions to this report.

Appendix V: Accessible Data

Data Tables

Accessible Data for Figure 1: Food and Drug Administration's (FDA) Typical Drug Development and Approval Process

1. PRE-CLINICAL

- a. Testing on animals for toxicity.

2. INVESTIGATIONAL NEW DRUG APPLICATION

- a. Describes the manufacturer's plans for testing the drug in clinical trials.
- b. If approved by FDA, the manufacturer becomes the sponsor of an "existing IND."

3. CLINICAL TRIALS

a. Phase I

- i. Clinical trials test for safety and dosing ranges.
- ii. No. of patients: 20 to 80
- iii. Approximately 63.2% moved to phase II

b. Phase II

- i. Clinical trials test for efficacy in the patients that the drug is intended to treat.
- ii. No. of patients: a few dozen to hundreds
- iii. Approximately 30.7% moved to phase III

c. Phase III

- i. Clinical trials test for efficacy in the patients that the drug is intended to treat.
- ii. No. of patients: hundreds to thousands
- iii. Approximately 58.1% moved to the new drug application process

4. REVIEW/APPROVAL PROCESS

a. New drug application review

- i. Once the drug has successfully completed the phase III trials, the manufacturer generally submits a new drug application to FDA.
- ii. Approximately 85.3% are approved

b. FDA approval results

- i. FDA either approves or denies approval for the drug or biologic for marketing and sales in the U.S.

Source: GAO analysis of FDA data and a 2016 collaborative study by Biotechnology Innovation Organization, Biomedtracker, and Amplion.a | GAO-17-564

Accessible Data for Figure 2: Types of Expanded Access Requests that Occur throughout the Food and Drug Administration's (FDA) Typical Drug Development and Approval Process

1. CLINICAL TRIALS

a. Phase I

- i. Drugs tested for safety and dosing ranges on 20 to 80 patients

b. Phase II

- i. Drugs tested for efficacy on a few dozen to hundreds of patients

c. Phase III

- i. Drugs tested for efficacy on hundreds to thousands of patients

2. REVIEW/APPROVAL PROCESS

- a. New drug application review
- b. FDA approval results
 - i. On average, 9.6% of drugs starting at phase I are approved

Single-patient expanded access requests (emergency and non-emergency) can generally occur during or after phases I, II, or III clinical trials.

Intermediate expanded access requests are generally initiated during or after phase II clinical trials.

Treatment expanded access requests are generally initiated during phase III clinical trials or once clinical trials are complete when a manufacturer is pursuing FDA's approval for marketing in the U.S.

Source: GAO analysis of FDA data. | GAO-17-564

Accessible Data for Figure 3: Expanded Access Treatment Protocol Example

- 1. Clinical trials
 - a. Phase I
 - i. Drugs tested for safety and dosing ranges on 20 to 80 patients
 - b. Phase II
 - i. Drugs tested for efficacy on a few dozen to hundreds of patients
 - c. Phase III
 - i. Drugs tested for efficacy on hundreds to thousands of patients

2. REVIEW/APPROVAL PROCESS

a. New drug application review

i. Stakeholder roles and responsibilities

1. Manufacturer submits a Form FDA 1571 notifying FDA that it is amending its existing IND. If allowed to proceed, manufacturer collects and submits adverse events data to FDA.
2. FDA has 30 days to review the request.
3. Physician requests access to the drug from the manufacturer, treats one or more patients, and submits adverse events data to the manufacturer.
4. IRB reviews and approves the treatment plan.

b. FDA approval results

- i. On average, 9.6% of drugs starting at phase I are approved

Accessible Data for Figure 4: Expanded Access Single-Patient IND Example

1. CLINICAL TRIALS

a. Phase I

- i. Drugs tested for safety and dosing ranges on 20 to 80 patients

b. Phase II

- i. Drugs tested for efficacy on a few dozen to hundreds of patients
- ii. Stakeholder roles and responsibilities
 1. Physician requests a letter of authorization from the drug manufacturer and, if obtained,

submits Form FDA 3926 or Form FDA 1571 request to FDA. If allowed to proceed, physician obtains IRB approval of treatment plan, treats the patient, and submits summary of results and adverse events data to FDA.

2. Manufacturer decides whether it will allow the patient access to the drug.
3. FDA has 30 days to review the request.
4. IRB reviews and approves the treatment plan.

c. Phase III

- i. Drugs tested for efficacy on hundreds to thousands of patients

2. REVIEW/APPROVAL PROCESS

- a. New drug application review
- b. FDA approval results
 - i. On average, 9.6% of drugs starting at phase I are approved

Agency Comment Letters

Text of Appendix III: Comments from the Department of Health & Human Services

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DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation Washington, DC 20201

JUN 1 2017

John Dicken

Director, Health Care

U.S. Government Accountability Office 441 G Street NW

Washington, DC 20548 Dear Mr. Dickens:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "Investigational New Drugs: FDA Has Taken Steps to Improve the Expanded Access Program but Needs to Clarify How Adverse Events Data Are Used" (GAO-17-564).

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

Sincerely,

Barbara Pisaro Clark

Acting Assistant Secretary for Legislation

Attachment

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GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: INVESTIGATIONAL NEW DRUGS: FDA HAS TAKEN STEPS TO IMPROVE THE EXPANDED ACCESS PROGRAM BUT NEEDS TO CLARIFY HOW ADVERSE EVENTS DATA ARE USED (GAO-17-564)

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

The Food and Drug Administration (FDA) is committed to increasing awareness of and knowledge about its expanded access process and the procedures for obtaining access to investigational drugs, and appreciates GAO's recognition of its efforts in this area. For over two decades, FDA

has had in place a system that strikes a careful balance between helping patients gain access to investigational drugs, on the one hand, and helping to ensure patient safety and preserving the clinical trial development process on the other. As GAO notes, through its expanded access process, from fiscal years 2012-2015, FDA has conducted timely reviews of nearly 5,800 expanded access requests, and allowed nearly all of them (99 percent) to proceed .

FDA also has made numerous improvements to the expanded access process to make it easier to navigate and more accessible to patients, physicians, and other stakeholders. FDA established an expedited telephone process for daytime and after-hours emergency requests for expanded access, and revamped the regulations regarding expanded access to investigational drugs to make the process and responsibilities of physicians more clear and concise. In June 2016, in response to feedback from physicians that completing the expanded access form (Form FDA 1571) was time-consuming, FDA released a simple new form (Form FDA 3926) for individual patient expanded access INDs. As GAO notes in its report, this form is estimated to take 45 minutes to complete and requires much less information than the previous submission process. Along with the new form, FDA released step-by-step instructions on how to complete it. Almost immediately, physicians began to take advantage of the new form. FDA also finalized a Questions and Answers guidance that explains what expanded access is, when and how to request expanded access, and the type of information that should be included in requests. At the same time, FDA released another guidance that explains the regulations regarding when and how patients may be charged for investigational drugs. Simultaneously, FDA revamped its expanded access website and produced Fact Sheets for physicians and patients. In addition to web pages directed specifically toward patients, physicians and industry, FDA has staff available to assist physicians and patients in understanding how to apply for expanded access.

GAO Recommendation

To help FDA meet its goal of facilitating expanded access to investigational drugs by patients with serious or life-threatening diseases or conditions when appropriate, the Commissioner of FDA should clearly communicate how the agency will use adverse event data from expanded access use when reviewing drugs and biologics for approval for marketing and sale in the United States.

HHS Response

HHS understands that the review of adverse event reports that result from expanded access use must be interpreted with caution, and the Agency is gratified that GAO has recognized that such data help FDA collect meaningful information about the use of investigational drugs. Indeed, Question 25 of FDA's Questions and Answers guidance on expanded access seeks to clarify how the Agency interprets adverse events that arise during expanded access. As GAO notes, citing

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GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: INVESTIGATIONAL NEW DRUGS: FDA HAS TAKEN STEPS TO IMPROVE THE EXPANDED ACCESS PROGRAM BUT NEEDS TO CLARIFY HOW ADVERSE EVENTS DATA ARE USED (GAO-17-564)

FDA data, there have been only two instances in which adverse events from expanded access use contributed to a decision to put development of an investigational drug on a partial clinical hold. In both instances, the development of the drugs continued after issues were addressed and the holds were lifted. While these data do not support the assertions of some manufacturers that such data may influence FDA in making final approval decisions, FDA nevertheless concurs with GAO's recommendation, recognizing that additional clarity on how the Agency uses adverse event data from expanded access use may help to allay these concerns.

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