



November 2021

DRUG DEVELOPMENT

Pathway for
Approving
Antibacterial and
Antifungal Drugs for
Patients with Limited
Treatment Options is
Infrequently Used



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Why GAO Did This Study

It is estimated that at least 2.8 million antibacterial and antifungal-resistant infections occur each year in the United States, and more than 35,000 people die as a result, according to the Centers for Disease Control and Prevention. The development of new antibacterial and antifungal treatments is one strategy to address the threat of antimicrobial resistance. The 21st Century Cures Act, enacted in 2016, established LPAD to help facilitate the approval of certain antibacterial and antifungal drugs. FDA oversees the approval of such drugs.

The 21st Century Cures Act includes a provision for GAO to review and report on FDA’s LPAD activities. This report describes (1) the extent to which LPAD changes FDA’s drug approval process, (2) the extent to which drug developers have sought to use LPAD for drugs under development, and (3) stakeholders’ and FDA’s views on the effectiveness of LPAD in benefiting the development and approval of antibacterial and antifungal drugs.

GAO reviewed FDA guidance documents; documentation from the approval process; and drug developers’ written statements to investors and FDA on LPAD. GAO also interviewed FDA officials and obtained information from 10 stakeholders selected because they sought approval for a drug through LPAD, considered using LPAD, or provided written comment to FDA on LPAD. These included two industry associations, one think tank, and seven drug developers.

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

View [GAO-22-105042](#). For more information, contact Mary Denigan-Macauley at (202) 512-7114 or deniganmacauleym@gao.gov.

DRUG DEVELOPMENT

Pathway for Approving Antibacterial and Antifungal Drugs for Patients with Limited Treatment Options is Infrequently Used

What GAO Found

Antibacterial and antifungal infections resistant to available drugs are a serious public health challenge. However, the number of drugs under development may be insufficient to meet this threat, in part because developers face economic and other challenges in developing drugs for these conditions, many of which are still relatively rare. The Food and Drug Administration (FDA) may use a certain pathway—known as the limited population pathway for antibacterial and antifungal drugs (LPAD)—to approve drugs intended to treat serious or life-threatening infections that affect a limited group of patients and are not adequately addressed by available therapy. LPAD does not fundamentally change FDA’s drug approval process, but it does provide tools that can help the agency accept greater risk and uncertainty when deciding to approve a drug for these otherwise difficult to treat infections, according to FDA officials. As a result, officials say FDA may approve a drug for a limited population because of the potential benefits for these patients, despite risks that would be unacceptable if the drug was intended to treat a broader population.

GAO’s review of FDA documentation shows that since LPAD was established in 2016, drug developers have formally requested approval under LPAD for four drugs, two of which were approved:

Two Drugs Approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD), as of June 2021

Drug Name	Condition approved to treat	Population with condition
Arikayce	Treatment of a bacterial infection in the lung called refractory Mycobacterium avium complex lung disease	Fewer than 27 per 100,000 persons older than 60 years of age
Pretomanid	Treatment of types of highly drug-resistant tuberculosis	123 cases reported in the United States in 2017

Source: Food and Drug Administration and Centers for Disease Control and Prevention. | [GAO-22-105042](#)

FDA and stakeholders agreed that LPAD’s effect on the drug pipeline could be limited because the pathway does not address the economic challenges facing the development of these products. For example, according to stakeholders, given the limited market for such drugs, sales revenue can be insufficient to cover development costs, making it difficult for companies to survive in the antibacterial and antifungal drug market. In March 2020, GAO reported on similar challenges and recommended that the Department of Health and Human Services (HHS) develop a strategy to further incentivize the development of new treatments for antibiotic-resistant infections, including the use of post-market financial incentives, which could include rewards for market entry or reimbursement reform. HHS did not concur with this recommendation, and as of June 2021, the agency indicated that it was still examining the issue and this recommendation had not been implemented.

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Abbreviations

CDC	Centers for Disease Control and Prevention
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IND	investigational new drug
LPAD	limited population pathway for antibacterial and antifungal drugs
MAC	Mycobacterium avium complex

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November 19, 2021

The Honorable Patty Murray
Chairman
The Honorable Richard Burr
Ranking Member
Committee on Health, Education, Labor & Pensions
United States Senate

The Honorable Frank Pallone
Chairman
The Honorable Cathy McMorris Rodgers
Republican Leader
Committee on Energy & Commerce
House of Representatives

Antimicrobial resistance—the ability of microorganisms such as bacteria or fungi to resist the effects of a drug—is a serious public health challenge. It is estimated that at least 2.8 million antibacterial- and antifungal-resistant infections occur each year in the United States, and more than 35,000 people die as a result, according to the Centers for Disease Control and Prevention (CDC).¹ The development of new antibacterial and antifungal treatments is one strategy to address the threat of antimicrobial resistance; however, as we previously reported, experts are concerned that the number of antibacterial and antifungal drugs in development is insufficient to meet this threat.²

Like other types of drugs, the development of antibacterial and antifungal drugs requires substantial investment and many years—typically 10 to 15 years—before they are ready to be reviewed by the Food and Drug Administration (FDA) to be approved for the U.S. market. Drug sponsors

¹Department of Health and Human Services, Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States, 2019*, (Atlanta, GA: Dec. 2019).

²We use the term “drug” in this report to refer to both chemically synthesized drugs and therapeutic biological products. Biological products—which include vaccines, blood products, and proteins, among other things—are derived from living sources such as humans, animals, and microorganisms. See 42 U.S.C. § 262(i)(1) and 21 C.F.R. § 600.3(h) (2020).

GAO, *Antibiotic Resistance: Additional Federal Actions Needed to Better Determine Magnitude and Reduce Impact*, [GAO-20-341](#) (Washington, D.C.: Mar. 30, 2020).

must develop these drugs and then test their safety and effectiveness through clinical trials.³ However, antibacterial and antifungal drug sponsors face additional challenges that may limit development. These include economic challenges—such as poor return on investment due to efforts aimed at slowing antimicrobial resistance that call for limiting the use of such drugs—and scientific challenges—such as difficulties in enrolling sufficient numbers of patients with rare infections into clinical trials.

The 21st Century Cures Act, enacted in 2016, contained several provisions to address antimicrobial resistance.⁴ Among these provisions, it established the limited population pathway for antibacterial and antifungal drugs (LPAD) to facilitate the development and approval of certain antibacterial and antifungal drugs.⁵ Following the release of draft guidance to industry on LPAD in June 2018 and the solicitation of stakeholder comments, FDA released its final LPAD guidance in August 2020 outlining eligibility criteria, processes, and other general considerations for demonstrating the safety and effectiveness of antibacterial and antifungal drugs that are intended for a limited population.⁶

The 21st Century Cures Act also includes a provision for us to review and report on LPAD.⁷ This report describes:

1. The extent to which LPAD changes FDA's drug approval process;
2. The extent to which drug sponsors have sought to use LPAD for drugs under development; and
3. Stakeholders' and FDA's views on the effectiveness of LPAD in benefiting the development and approval of antibacterial and antifungal drugs.

³A drug sponsor—sometimes called a drug developer—is the person or entity that assumes responsibility for the development of a new drug, including responsibility for complying with applicable laws and regulations.

⁴Pub. L. No. 114-255, 130 Stat. 1033 (2016).

⁵See 21 U.S.C. § 356(h).

⁶Department of Health and Human Services, Food and Drug Administration, *Limited Population Pathway for Antibacterial and Antifungal Drugs (Guidance for Industry)* (Silver Spring, Md.: Aug. 2020).

⁷Pub. L. No. 114-255, § 3042, 130 Stat. at 1114.

To examine all three objectives, and in particular to describe the extent to which LPAD changes FDA's drug approval process, we analyzed relevant laws and FDA guidance and interviewed FDA officials. To describe how many drug sponsors have sought to use LPAD for drugs under development, we obtained and analyzed documentation from FDA on the drug approval process for those drugs reviewed under LPAD. To identify how many drug sponsors have considered using LPAD, we obtained written responses from FDA and relied on public sources, including reviewing the annual reports publicly traded companies must file with the U.S. Securities and Exchange Commission. We supplemented these publicly available sources with information gathered from a prior GAO report and interviews conducted with drug sponsors.⁸ In our count, we included drug sponsors that described their consideration of seeking approval under LPAD in reference to a specific drug under development, and we excluded drug sponsors that solely mentioned LPAD as part of the general regulatory environment. Due to available information, our count of how many drug sponsors have considered using LPAD may be incomplete.

To describe stakeholders' and FDA's views on the effectiveness of LPAD in benefiting the development of antibacterial and antifungal drugs, we interviewed FDA officials and we identified stakeholders for interview to include multiple perspectives in the industry.⁹ Specifically, we interviewed the two industry associations and one think tank that each submitted comments to FDA on the draft LPAD guidance and could provide a high-level view of the antibacterial and antifungal drug development landscape.¹⁰ We also interviewed or reviewed written responses from seven drug sponsors—identified from our list of drug sponsors that considered using LPAD—with varying degrees of experience with LPAD to represent their own perspectives on, and experiences with, LPAD

⁸[GAO-20-341](#).

⁹We refer to representatives of stakeholder groups as "stakeholders" in this report.

¹⁰We interviewed representatives of Biotechnology Innovation Organization, Pharmaceutical Research and Manufacturers of America, and Pew Charitable Trusts. The other industry association that commented on the draft guidance is no longer in existence and was excluded. Additionally, one provider association commented on the draft guidance, but did not respond to our outreach. Department of Health and Human Services, Food and Drug Administration. *Limited Population Pathway for Antibacterial and Antifungal Drugs (Draft Guidance for Industry)* (Silver Spring, Md.: June 2018).

specific to their organization’s development pipeline.¹¹ Due to the targeted eligibility of the pathway, we purposively selected stakeholders with specific knowledge of LPAD. To supplement those interviews, we reviewed documentation of interviews with similar stakeholders from GAO’s recent report on antibiotic resistance that touched upon LPAD.¹² We also analyzed the statements of stakeholders that provided input on the LPAD guidance to FDA through comment letters or statements and presentations made in FDA’s 2019 public meeting on LPAD.¹³ The views of the stakeholders interviewed cannot be generalized to all stakeholders.

We conducted this performance audit from February 2021 to November 2021 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Drug Development Process and Approval Standards

FDA is responsible for ensuring the drugs marketed in the United States are safe and effective, which it does by evaluating data collected during the drug development process. The drug development process can involve a number of steps, including pre-clinical laboratory and animal testing and clinical testing in human volunteers to determine a drug’s safety and effectiveness. Before a drug can be tested on humans, the drug sponsor must submit an investigational new drug (IND) application for FDA to review. Once an IND goes into effect, the drug typically moves through three phases of clinical trials.¹⁴

- Phase I clinical trials generally test the safety of the drug on about 20 to 100 healthy volunteers. The goal of this phase is to determine how

¹¹We interviewed or received written responses from representatives of CorMedix, Insmad, Matinas BioPharma, Microbiotix, Scynexis, TB Alliance, and Venatorx Pharmaceuticals.

¹²[GAO-20-341](#).

¹³See 83 Fed. Reg. 27,616 (June 13, 2018) (announcement of draft guidance) and 84 Fed. Reg. 12,621 (Apr. 2, 2019) (announcement of public meeting).

¹⁴21 C.F.R. § 312.21 (2020). An IND generally goes into effect 30 calendar days after FDA receives it, unless FDA places the IND on clinical hold. See 21 C.F.R. § 312.40(b) (2020).

the drug is metabolized and side effects of increasing doses, as well as to gain early evidence of effectiveness.

- Phase II clinical trials assess the drug's side effects and effectiveness on several hundred people who have the disease or condition for which the drug is being developed, typically through comparison with a control group. The goal of this phase is to determine common short-term side effects and risks associated with the drug.
- Phase III clinical trials are expanded, controlled and uncontrolled studies that are intended to gather additional information about safety and effectiveness. These studies typically consist of 300 to 3,000 participants and provide the necessary information to evaluate the overall risks and benefits of the drug.

Once phase III clinical trials are complete, drug sponsors may submit a marketing application to FDA to seek approval to market the drug in the United States. In making approval decisions, FDA reviewers conduct a benefit-risk assessment in which they determine whether the benefits of the product outweigh its risks. Specifically, the FDA reviewers evaluate evidence from the clinical trials to determine if there is substantial evidence of effectiveness and sufficient information to conclude that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling.¹⁵ FDA approval standards require that marketing applications include data from adequate and well-controlled clinical trials to provide the agency with the substantial evidence required for an approval. Such trials allow for valid comparisons with a control group to provide for a quantitative assessment of the drug effect and have methods of assigning participants to treatment and control groups that minimize bias, among other things.¹⁶ In many situations, FDA requires two adequate and well-controlled trials to establish effectiveness. However, in certain circumstances, FDA may determine that a streamlined development program with fewer or smaller clinical trials is sufficient to meet this standard of evidence.

Through the use of multiple expedited programs, FDA has authority to facilitate drug development and speed the application review process. Several of these programs apply to new drugs intended to treat a serious condition and address an unmet need.

¹⁵See 21 U.S.C. § 355(d).

¹⁶See 21 C.F.R. § 314.126 (2020).

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- For example, fast track designation facilitates the development and expedites the review of drugs intended to treat serious conditions and that demonstrate the potential to address unmet medical needs such as by providing a new therapy where none exists or by providing a therapy that may be potentially better than available therapies.¹⁷ The program does this by providing for more frequent meetings with FDA and allowing drug sponsors to submit sections of the application for rolling review by FDA as they are completed.
 - As another example, an application can receive a priority review designation from FDA if the drug would provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious condition when compared to available therapies.¹⁸ A priority review designation generally reduces FDA's goal review time from 10 months to 6 months.¹⁹

For all applications, over the course of the drug development process, both before and after a marketing application is submitted, drug sponsors can routinely solicit feedback from FDA on scientific and regulatory issues. Dependent upon the drug sponsor's requests, FDA will provide advice on specific aspects of the development program, such as whether the design of a clinical trial is likely to produce the data and information needed to meet the requirements for a marketing application. Discussions can also focus on eligibility for expedited programs or the validity of clinical endpoints (i.e., outcome measures used to determine the effectiveness of the drug), among other things.

LPAD Features and Implementation

LPAD facilitates the development and approval of antibacterial and antifungal drugs to treat serious or life-threatening infections in limited populations of patients with unmet needs. FDA guidance states that the limited populations targeted by LPAD are groups of patients that are

¹⁷See 21 U.S.C. § 356(b).

¹⁸A small number of applications receive priority review designation because the drug sponsor uses a priority review voucher. FDA awards priority review vouchers to drug sponsors that develop and receive approval for certain products for tropical diseases, rare pediatric diseases, and material threat medical countermeasures. The drug sponsor may use the priority review voucher on a future application for any disease or condition.

¹⁹For new drugs that do not contain a new molecular entity, FDA's goal is to review and act on 90 percent of standard applications within 10 months and 90 percent of priority applications within 6 months of receipt. For original biologics and new drugs that contain a new molecular entity, FDA's goal is to review and act on 90 percent of standard applications within 10 months following a 60-day filing period (a total of 12 months from receipt). Priority review reduces this time to 6 months following the filing period (a total of 8 months from receipt).

limited in a way that is clinically relevant to health care providers. For example, people with a specific subset of a broader type of infection—such as the relatively small number of patients with a specific type of highly treatment-resistant tuberculosis—could be considered a limited population. However, the guidance states that the limited population does not need to be below a specific numerical threshold. Unmet needs refer to conditions or diseases whose treatment or diagnosis is not addressed adequately by available therapy.

Drugs approved under LPAD must meet the same standards for approval as other approved drugs. That is, there must be substantial evidence of effectiveness for the drug's intended use and sufficient information to conclude that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. FDA's safety and effectiveness determination for approval under LPAD must reflect the benefit-risk assessment of the drug in the intended limited population, taking into account the severity, rarity, or prevalence of the infection the drug is intended to treat and the lack of alternatives available for the patient population. To communicate the intended limited population to the health care community, the labeling and advertising for drugs approved under LPAD must convey that the drug has been shown to be safe and effective for use only in a limited population.²⁰

As with any other drug under development, drug sponsors may consult with FDA prior to seeking approval on specific aspects of the development program. Under LPAD, FDA is required to provide prompt advice to drug sponsors attempting to use the pathway to enable them to plan a development program to obtain the data necessary for an LPAD approval. The LPAD guidance states that early and frequent communications between FDA and drug sponsors can help reduce overall drug development timelines. While FDA recommends discussing LPAD early on in development, in order to be considered for LPAD approval, the drug sponsor must make a written request to FDA when the marketing application is submitted or at any time during the review of the application. However, according to the LPAD guidance, if FDA concludes

²⁰Drugs approved under LPAD must have labeling and advertising that contain the statement "Limited Population" in a prominent manner and adjacent to, but not more prominent than, the name of the drug. The prescribing information for drugs approved under LPAD also must include the phrase "This drug is indicated for use in a limited and specific population of patients." 21 U.S.C. § 356(h)(3)(A).

during its review of an application that LPAD would be appropriate for the drug, FDA will recommend it to the drug sponsor.

LPAD Does Not Fundamentally Change the Approval Process but Helps FDA Accept Greater Risk and Uncertainty in Determining Approval

LPAD does not fundamentally change the agency's drug approval process, according to FDA officials. For example, while FDA expects that drugs approved under LPAD may have fewer or smaller clinical trials, LPAD does not inherently streamline the drug development process.²¹ However, agency officials said that for the narrowly defined circumstances when LPAD is applicable, the pathway provides FDA with the ability to accept greater risk and uncertainty with a drug when evaluating a marketing application for approval. Specifically:

- The LPAD statute explicitly directs FDA to consider whether the benefits of a drug in the intended limited population outweigh the risks as part of its benefit-risk assessment of the drug's safety and effectiveness evidence. As a result, FDA officials said the agency may take on more risk and uncertainty—for example by making this determination with smaller clinical trials—when determining approval for the limited population compared with a broader population.
- LPAD's requirement for drug labeling and advertising to include language noting that the drug was approved under the pathway provides FDA with the ability to manage risk by facilitating health care providers' understanding of the limited population and the conditions under which the drug was approved, according to agency officials.

According to FDA officials, although LPAD does not represent a fundamental change to the approval process and still requires drug sponsors to provide substantial evidence of the drug's effectiveness and sufficient information to conclude that the drug is safe, this pathway might mean the difference between receiving approval or not for an eligible drug. Prior to LPAD, FDA's drug approval process already included a benefit-risk assessment, which considers the severity of the underlying condition and patient unmet needs, and drug labeling was already required to include essential scientific information needed for the safe and

²¹The LPAD guidance refers to streamlined development strategies; however, agency officials said that drug sponsors may also use such strategies even if a drug is not reviewed under LPAD. Additionally, LPAD does not change how the agency advises drug sponsors throughout drug development, according to the agency. FDA determined that to provide prompt advice to drug sponsors—as required by LPAD—the agency would abide by the standard procedures for communication that the agency follows for any drug.

effective use of the drug.²² However, FDA officials said LPAD made such requirements explicit and more straightforward to implement for antibacterial and antifungal drugs intended for limited populations of patients with unmet needs. For example, FDA officials stated that without the labeling authority under LPAD, the agency might otherwise consider additional precautions when approving these drugs, for example, by requiring the drug sponsor to implement a risk evaluation and mitigation strategy designed to help ensure that the drug's use is limited to its approved indications in light of a specific serious risk(s).²³

Though LPAD does not offer financial incentives that would help drug sponsors to develop their drugs, drug sponsors that seek approval under LPAD may also be eligible for other FDA programs that expedite development and review or provide other financial incentives. For example, antibacterial and antifungal drugs eligible for LPAD could also receive qualified infectious disease product designation—which may qualify the drug for a 5-year extension of exclusivity that delays or prohibits the approval of competitor drugs—and fast track or priority review designation—which facilitate development and shorten FDA's goal review time, respectively.

Drug Sponsors Have Sought to Use LPAD for Four Drugs, Leading to Two Approvals

Our review of FDA documentation shows that as of June 2021, drug sponsors had formally requested LPAD for four drugs. Two of these drugs were approved under LPAD, and the other two drugs were not approved under LPAD, though one was approved for another indication, outside of LPAD.

For the two drugs approved under LPAD—Pretomanid and Arikayce—the pathway helped enable the approval of both drugs because the benefit-risk assessment for these treatments only supported use in a limited population of patients, according to FDA's approval package. Both drugs treat life-threatening infections with an unmet need for treatment.

²²21 U.S.C. § 355(d); 21 C.F.R. § 201.56 (2020).

²³A risk evaluation and mitigation strategy is a drug safety program that FDA can require for certain drugs with serious safety concerns to help ensure the benefits of the drug outweigh its risks. See 21 U.S.C. § 355-1. According to FDA, most risk evaluation and mitigation strategies are designed to reinforce patients' and health care providers' behaviors and actions that support the safe use of the particular drug they cover. See, GAO, *Generic Drug Development: Stakeholders' Views of Risk Evaluation and Mitigation Strategies Differ*, [GAO-20-94](#) (Washington, D.C.: Oct. 15, 2019).

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- Pretomanid is indicated for treatment of specific types of highly treatment-resistant tuberculosis.²⁴ According to its review of the marketing application, FDA determined patients with these specific types of tuberculosis infection had an unmet need and constituted a limited patient population. In its assessment, FDA found that previously available treatments could include five to eight drugs for periods up to 2 years, with low reported treatment success rates—typically below 50 percent.²⁵ CDC reported that in the United States, 123 cases of multidrug-resistant tuberculosis were reported in 2017.²⁶ While FDA identified uncertainties with the drug sponsor’s methodology to demonstrate effectiveness, the agency determined the benefit to this high-need, limited patient population outweighed the risks of approval, according to FDA’s benefit-risk assessment.
 - Arikayce is indicated for treatment of a bacterial infection in the lung, called refractory *Mycobacterium avium* complex (MAC) lung disease in adults who have limited or no alternative treatment options.²⁷ According to its review of the marketing application, FDA determined this limited patient population with refractory MAC lung disease had an unmet need. In its assessment, FDA found that previously there was no FDA-approved drug to treat MAC lung disease, and reported success rates of other treatments ranged from 20 to 90 percent. The agency also identified that MAC lung disease represents about 80 percent of nontuberculous mycobacteria lung disease, which has an estimated prevalence of 26.7 per 100,000 persons older than 60 years of age. In addition to LPAD, the drug sponsor pursued accelerated approval, which allows FDA to approve a drug based on evidence of an effect on a surrogate endpoint or intermediate clinical

²⁴Pretomanid is indicated, as part of a combination with bedaquiline and linezolid, for the treatment of adults with pulmonary extensively drug resistant, treatment-intolerant or nonresponsive multidrug-resistant tuberculosis.

²⁵Treatment success means the patient was cured or the treatment was completed without evidence of failure, following the World Health Organization definitions.

²⁶Department of Health and Human Services, Centers for Disease Control and Prevention, *Reported Tuberculosis in the United States, 2017* (Atlanta, Ga.: Oct. 2018).

²⁷Arikayce is approved as part of a combination antibacterial drug regimen in patients with refractory disease, specifically those patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy.

endpoint that is reasonably likely to predict clinical benefit.²⁸ FDA found that there was a degree of uncertainty in the predictive value of the surrogate endpoint, but considered it acceptable for an accelerated approval in the limited population of patients because refractory MAC lung disease is a serious condition with an unmet medical need. In its benefit-risk assessment, FDA explicitly stated that the agency needed to use LPAD in order to support a positive benefit-risk balance and approve the drug.

For both Pretomanid and Arikayce, the clinical development was largely complete before LPAD was established in 2016. Therefore, neither drug sponsor could have planned for LPAD approval during drug development, as their phase III clinical trials started in 2015, prior to the establishment of LPAD. According to the drug sponsors, they made the request for LPAD after FDA suggested it for their consideration and while their marketing applications were already under review. Both drug sponsors also took advantage of multiple other FDA programs to expedite the development and review process—such as fast track and priority review designation.²⁹ (See table 1.)

²⁸See 21 U.S.C. § 356(c). A surrogate endpoint is a laboratory measure or physical sign used as a substitute for a clinical endpoint that reasonably predicts a clinical benefit. For example, a drug sponsor may study whether a drug can lower blood pressure as a surrogate endpoint to predict whether the drug is effective in preventing strokes (the clinical endpoint). Through the use of surrogate endpoints, a drug sponsor may be able to demonstrate the effect of a new drug based on smaller and shorter trials than would be required to prove the drug's effectiveness on a clinical endpoint. See Department of Health and Human Services, Food and Drug Administration, *Expedited Programs for Serious Conditions – Drugs and Biologics (Guidance for Industry)* (Silver Spring, Md.: May 2014). See also GAO, *New Drug Approval: FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints*, [GAO-09-866](#) (Washington, D.C.: Sept. 23, 2009).

²⁹Arikayce qualified for four of FDA's expedited programs (accelerated approval, fast track designation, breakthrough therapy designation, and priority review designation) while Pretomanid qualified for two of these programs (fast track designation and priority review designation). In addition, Arikayce and Pretomanid both qualified for two other FDA programs that provide financial incentives to develop certain types of drugs (qualified infectious disease product designation and orphan drug designation).

Table 1: Two Drugs Approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD), as of June 2021

	Drugs approved under LPAD	
	Arikayce	Pretomanid
Condition approved to treat	Treatment of refractory Mycobacterium avium complex lung disease as part of a combination antibacterial regimen	Treatment of pulmonary extensively drug-resistant and treatment-intolerant/nonresponsive multidrug-resistant tuberculosis
Drug sponsor submits application to start clinical trials ^a	Feb 17, 2011	April 28, 2005
Drug sponsor submits marketing application	March 28, 2018	Dec 14, 2018
Drug sponsor submits LPAD written request	Sept 13, 2018	June 5, 2019
Food and Drug Administration (FDA) approves marketing application and LPAD response	Sept 28, 2018	Aug 14, 2019
Years between submission of application to start clinical trials and FDA's approval	7.6	14.3

Source: GAO analysis of documents from FDA. | GAO-22-105042

^aClinical trials may begin 30 days after a drug sponsor has submitted an investigational new drug application.

The sponsor of a third drug, Zemdri, sought, but did not receive, LPAD approval for treatment of bloodstream infections caused by certain drug-resistant bacteria, according to the sponsor's disclosures to investors. These bloodstream infections have limited treatments and mortality rates of approximately 40 percent to 50 percent. However, the Antimicrobial Drugs Advisory Committee—a body of experts that reviews safety and effectiveness data of antimicrobial drugs and makes recommendations to FDA—advised FDA not to approve Zemdri for this indication because the data did not meet FDA's standards for substantial evidence of safety and effectiveness. FDA officials reported that Zemdri's development program illustrates the challenges inherent in developing a new antibacterial drug—including the difficulty of enrolling patients with a rare condition into a clinical trial.³⁰ For example, the FDA officials noted that Zemdri's phase III trial for treatment of bloodstream infections was stopped early because

³⁰E. Cox, S. Nambiar, and L. Baden, "Needed: Antimicrobial Development," *New England Journal of Medicine*, vol. 380, no. 8 (2019).

Previously, we reported that enrolling patients in clinical trials was one challenge facing antibacterial and antifungal development. Certain types of antibiotic-resistant infections are rare and, therefore, drug developers and federal officials told us it can be difficult to find patients to enroll in clinical trials to test antibiotics that target resistant bacteria. [GAO-20-341](#).

of such enrollment challenges—enrolling 39 patients after screening 2,000.³¹

At the same time, the sponsor of Zemdri also requested and received approval outside of LPAD for treatment of complicated urinary tract infections—a more common infection with alternative treatments available. As a result, the drug can only be marketed for that indication, though federal law generally does not prohibit health care providers from prescribing approved drugs off-label for other purposes.³² The drug sponsor had indicated to investors that it was unable to raise sufficient funds to market the drug, and less than a year after receiving approval for Zemdri to treat complicated urinary tract infections, in April 2019 the drug sponsor filed for bankruptcy. Another sponsor has since acquired the rights to the drug and continues to market it.

According to the drug sponsor, the fourth drug that requested approval under LPAD, DefenCath—intended to prevent catheter-related bloodstream infections in certain patients with kidney failure—was not approved by FDA. The drug sponsor stated to investors that FDA did not approve the marketing application due to deficiencies at the manufacturing facility; however, it stated that the agency did not otherwise identify deficiencies in the safety and effectiveness of the drug. According to drug sponsor statements to investors in September 2021, the drug sponsor was uncertain when it would address the manufacturing deficiencies and resubmit the application to FDA.

While the specific number of drug sponsors interested in pursuing approval under LPAD is unknown, FDA officials said that the interest from drug sponsors is consistent with the limited antibacterial and antifungal drug development pipeline.

Based on our review of drug sponsors' public statements to investors and interviews with drug sponsors, we identified at least eight additional drug sponsors that have considered using LPAD since the pathway was enacted.

³¹Cox, Nambiar, and Baden, "Needed: Antimicrobial Development."

³²Off-label prescribing is the use of a drug for a condition or patient population for which the drug has not been approved or in a manner that is inconsistent with information found in the drug's FDA-approved labeling.

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- Five drug sponsors indicated they were still considering LPAD for drugs under clinical development. These drugs are intended to target bacteria and fungi that have been categorized as urgent or serious threats by CDC. As of March 2021, four of these drug sponsors reported they were conducting clinical trials, and one was conducting earlier pre-clinical studies.
 - Three drug sponsors indicated they were no longer considering LPAD. In one case, the drug sponsor discontinued its clinical development program to conserve cash resources. The drug sponsors of the other two drugs continued development, but determined that LPAD was not applicable.
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Stakeholders Identified Concerns with LPAD; They and FDA Agreed Its Effects on Drug Development and Approval May be Limited

Stakeholders Expressed Concerns Related to FDA's Implementation of LPAD, though FDA Explained Why These Issues Remain

Of the 10 stakeholders we interviewed, five expressed concerns that LPAD had fallen short of their expectations. Specifically, four of these stakeholders said that they had anticipated that more than two drugs would have been approved by now if the pathway were effective. However, one stakeholder did acknowledge that there is not a large queue of antibacterial and antifungal drugs under development, so one would not expect a large number of approvals in this area. In response, FDA officials considered the two LPAD approvals to date to be successful uses of the pathway, which facilitated FDA's review and approval. They noted that LPAD is intended for a specific subset of products in one therapeutic area where the volume of new drugs in development is already low.

Stakeholders also expressed concerns on two aspects of LPAD, specifically the timeline of LPAD eligibility determination and the need for additional clarity in the guidance. FDA officials explained why the agency is unable to make changes to address these concerns.

Determination of LPAD
Eligibility

Stakeholders stated that because FDA does not determine LPAD eligibility until after a marketing application has been submitted, drug sponsors have more uncertainty during the drug development process, and this uncertainty limits the potential for drug sponsors to streamline their development programs. Specifically, of the 10 stakeholders that we interviewed, six stated they believed that eligibility for LPAD should be determined earlier in the development process, which could remove some uncertainty during that process. For example, five of these stakeholders said that having more certainty about whether a drug is eligible for LPAD would allow drug sponsors to plan more efficient clinical trials by enrolling fewer people or securing additional funding from investors. This in turn would benefit the drug sponsors, since streamlined development programs require the use of fewer resources. Four of these stakeholders stated that because FDA does not make the eligibility determination until after the marketing application is submitted, drug sponsors would not streamline development out of concern that it would not be sufficient for approval.

FDA officials stated that it is not possible to give drug sponsors a definitive determination of LPAD eligibility without reviewing the clinical data included in the marketing application, which FDA uses to conduct its benefit-risk assessment. FDA officials said that while they cannot make a definitive determination without these data, they may be able to share with drug sponsors whether the drug “may” be appropriate for LPAD based on the pathway’s criteria. Agency officials stated that if there is interest in developing a drug for a limited population, drug sponsors should ideally notify FDA of their intent to request LPAD during development. If drug sponsors do so, agency officials said that they will work with the drug sponsor to ensure that the population is clearly defined in a clinically meaningful way.

FDA officials added that regardless of whether the drug sponsor is interested in an LPAD approval, early in the development process, they discuss with drug sponsors which trial designs will provide interpretable data that will support approval of their products. Officials stated that they offer advice to drug sponsors to help them develop successful programs and that they will guide developers to the correct pathway as needed. While FDA officials acknowledged that drugs ultimately approved through LPAD may have streamlined development programs, they added that this streamlining is independent of the drug’s LPAD status. According to FDA, the number and types of studies necessary for approval are determined by the attributes of the product, such as whether it is addressing an

unmet need, and the patient population for which the drug will be indicated.

Clarity of LPAD Guidance

Of the 10 stakeholders we interviewed, eight noted the need for further clarification in the LPAD guidance. For example, five stakeholders said they would like FDA to add further clarification to the LPAD guidance by providing additional information on the types of trial designs and clinical data that would meet standards of approval. Additionally, three of these stakeholders said that there have been too few examples of LPAD approvals from which to learn how to use the pathway effectively.

FDA officials stated that the agency had attempted to provide greater clarity by including several examples in the LPAD guidance of trial designs and data that would meet standards of approval. Additionally, they stated that FDA provides examples of the types of drugs that might be eligible for LPAD in the guidance document. However, officials added that it is difficult to include further examples of hypothetical scenarios in the absence of specific drugs. FDA officials also stated that it is difficult to include the specificity that drug sponsors want within the guidance because of how broad the guidance needs to be. FDA officials noted that the agency publishes indication-specific guidance on trial designs and those recommendations may be utilized by drug sponsors pursuing approval under LPAD. Additionally, if a drug sponsor requests it, FDA officials said the agency will communicate with them to discuss issues of trial design and ensure that the limited population being targeted by the drug is defined in a clinically meaningful way. Several stakeholders also acknowledged that the broadness of the guidance was important for allowing FDA to exercise its authority with maximum flexibility. One stakeholder told us that if there were more specifics in the guidance, drug sponsors would likely seek to fit their development programs within these and would not utilize other possible methods. Thus, the broader guidance allows for greater flexibility in the development program as well.

FDA Believes It Is Too Early to Evaluate LPAD's Impact on the Development and Approval of Drugs, But Both the Agency and Stakeholders Expect Limited Effects

FDA officials stated there is currently too little data to conduct a formal evaluation of LPAD to determine if this pathway will facilitate development and approval of antibacterial and antifungal drugs. Additionally, officials noted that LPAD is simply one regulatory tool of many to support antibacterial and antifungal drug development and that evaluating its effectiveness will be difficult, as the agency may not be able to fully parse out its effects from those of other approval programs. FDA officials added that it was too soon to determine LPAD's overall effect on the number of antibacterial and antifungal drugs being developed, or if the drugs

approved through LPAD are having an effect on antibacterial and antifungal drug resistance.³³

However, FDA officials stated that, in light of our questions about LPAD, the agency plans to include an evaluation of the pathway in its next required biennial report to Congress.³⁴ They said the evaluation will consider the drug products approved under the pathway to date, agency officials' understanding of their utilization, and feedback FDA has received from drug sponsors and other stakeholders. Officials also stated that the report will likely identify what efforts in addition to LPAD are needed to support development of new antibacterial and antifungal drugs. FDA submitted the first of its required biennial reports on LPAD to Congress in 2018 and the next was due in 2020.³⁵ However, FDA officials said that, due to the agency's Coronavirus Disease 2019 pandemic response, the 2020 biennial report has been delayed. They anticipate issuing the report in the first quarter of 2022.

Regardless of whether an evaluation finds LPAD to be effective for its intended purpose, FDA and most stakeholders expect that LPAD could have a limited effect on the development of new antibacterial and antifungal drugs because it does not address the economic challenges facing these products. For example, five stakeholders reported that drug revenue was insufficient to cover development costs, making it difficult for companies to survive in the antibacterial and antifungal drug market. FDA's 2018 biennial report to Congress reported that efforts—beyond

³³FDA officials also noted it is too soon to tell whether a pathway similar to LPAD would be appropriate for other categories of drugs beyond antibacterials and antifungals. Stakeholders had mixed opinions on this issue. For example, one stakeholder said that FDA already had many of the authorities granted by LPAD and another stated that a similar pathway would be suitable for other categories of drugs treating unmet medical needs (e.g., brain cancer and pediatric drugs).

Even though FDA officials said it is too early to conduct a formal evaluation of LPAD's effect on antimicrobial resistance, FDA officials noted that the agency does not treat LPAD drugs any differently from other drugs in terms of monitoring antimicrobial resistance. FDA, in coordination with CDC, shared that the agencies coordinate monitoring on LPAD-approved drugs with the intention of making information public. More generally, CDC releases reports and data through multiple websites that provide updates on specific drug-resistant pathogens. See 42 U.S.C. § 247d-5(g) and (j).

³⁴In these reports, FDA is required to report on the number of requests for approval and the number of actual approvals under LPAD. 21 U.S.C. § 356(h)(9)(A).

³⁵In the 2018 report, FDA reported on its release of the draft guidance document and its efforts to engage with drug sponsors.

LPAD and other existing strategies—that address these economic obstacles can help strengthen the fragile development pipeline.

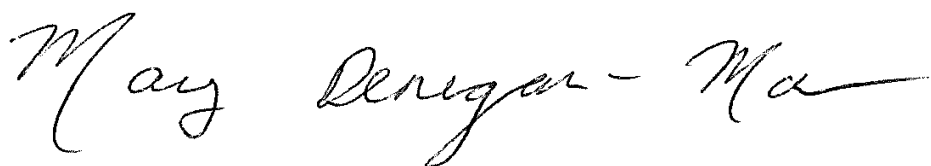
In March 2020, we reported on similar challenges and recommended that the Department of Health and Human Services (HHS) develop a strategy to further incentivize the development of new treatments for antibiotic-resistant infections, including through the use of post-market financial incentives, which could include rewards for market entry or reimbursement reform.³⁶ HHS did not concur with this recommendation, stating that the agency was still conducting analyses at the time for their forthcoming strategic framework to see whether post-market incentives should be included. We maintain that it is important that HHS not delay the development of such a strategic framework, which would be the initial step toward the creation of these incentives. As of June 2021, the agency indicated that it was still examining the issue and this recommendation had not been implemented.

Agency Comments

We provided a draft of this report to HHS for comment. HHS provided technical comments, which we incorporated as appropriate.

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

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or at deniganmacauleym@gao.gov. Contact points for our Office of Congressional Relations and Office of Public Affairs can be found on the last page of this report. Other major contributors to this report are listed in appendix I.



Mary Denigan-Macauley
Director, Health Care

³⁶See [GAO-20-341](#).

Appendix I: GAO Contact and Staff Acknowledgments

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Staff Acknowledgments

In addition to the contact named above, William Hadley (Assistant Director), Kelly Krinn (Analyst-in-Charge), Sam Amrhein, Sonia Chakrabarty, Justin Cubilo, Kaitlin Farquharson, and Jeanne Murphy-Stone made key contributions to this report.

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