Limited Population Pathway for Antibacterial and Antifungal Drugs

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2020
Procedural

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Contains Nonbinding Recommendations

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Limited Population Pathway for Antibacterial and Antifungal Drugs Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information on the implementation of section 506(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), added by section 3042 of the 21st Century Cures Act,[2] which established the limited population pathway for antibacterial and antifungal drugs (LPAD pathway).[3]

Section 506(h)(5) of the FD&C Act requires FDA to issue guidance "describing criteria, processes, and other general considerations for demonstrating the safety and effectiveness of limited population antibacterial and antifungal drugs." This guidance provides this information and is intended to assist sponsors[4] in the development of certain new antibacterial and antifungal drugs for approval under the LPAD pathway. This guidance also is intended to assist applicants

[1] This guidance has been prepared by the Office of Infectious Diseases and Office of New Drug Policy in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] Public Law 114-255, 130 Stat. 1033 (2016) (21 U.S.C. 356).

[3] For the purposes of this guidance, all references to *drugs*, *drug products*, and *products* include both human drug and biological products regulated by CDER and CBER unless otherwise specified.

[4] For purposes of this guidance, the term *sponsor* and *applicant* includes any sponsor of an investigational new drug application (IND) or applicant for a new drug application or biologics license application under section 505 of the FD&C Act or section 351 of the Public Health Service Act, respectively.

in developing labeling, including prescribing information, patient labeling, and carton/container labeling, that incorporates certain statements required by section 506(h).[5]

This guidance does not address specific recommendations on the design of clinical trials for drugs developed under the LPAD pathway. That topic is addressed in the guidance for industry *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases* (August 2017) (Unmet Medical Need guidance).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The decline in antibacterial drug research and development as serious antibacterial drug resistant infections increase is a critical public health and patient care concern. As described in the Unmet Medical Need guidance, there are a number of challenges associated with conducting clinical trials to evaluate antibacterial drugs for the treatment of patients with serious bacterial diseases.[6] Similar challenges are also associated with the development of new antifungal drugs for the treatment of serious fungal diseases.

Title VIII of the Food and Drug Administration Safety and Innovation Act, titled Generating Antibiotic Incentives Now (GAIN), added section 505E to the FD&C Act (21 U.S.C. 355f), offering incentives for the development of antibacterial and antifungal drug products that treat serious or life-threatening infections. Even with these incentives, challenges remain. FDA is committed to using the tools at its disposal, including the LPAD pathway, to help encourage the development of safe and effective drug products that address unmet needs of patients with serious bacterial and fungal infections.

[5] Except in certain instances discussed in this guidance, the statutory LPAD pathway framework does not alter the statutory or regulatory requirements for drugs, nor does it affect the recommendations or the applicability of FDA's guidance documents, including the guidance for industry *Microbiology Data for Systemic Antibacterial Drugs — Development, Analysis, and Presentation* (February 2018). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[6] For purposes of this guidance, FDA considers infections to be types of diseases or conditions. The terms *condition*, *disease*, and *infection* are used interchangeably.

III. LPAD PATHWAY DEFINED

Section 506(h)(1) of the FD&C Act provides that FDA may approve an antibacterial or antifungal drug,[7] alone or in combination with one or more other drugs, under the LPAD pathway, if the following apply:

- The drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs;
- The standards for approval under section 505(c) and (d) of the FD&C Act (21 U.S.C. 355) or the standards for licensure under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), as applicable, are met; and
- FDA receives a written request from the sponsor to approve the drug as a limited population drug (see section VI.B., Written Request for Approval Under the LPAD Pathway).

As discussed in greater detail in section V., Considerations for Approval of Drugs Under the LPAD Pathway, development programs for drugs eligible for approval under the LPAD pathway may follow the streamlined approaches described in the Unmet Medical Need guidance. A streamlined clinical development program for a limited population may involve smaller, shorter, or fewer clinical trials. FDA encourages sponsors to discuss with FDA their proposed designs of streamlined clinical trials early in the process.

Section 506(h)(3) also imposes specific labeling requirements and a requirement for presubmission of promotional materials for drugs approved under the LPAD pathway.

There may be cases when a drug is approved under the LPAD pathway for certain indications and may be approved under a non-LPAD pathway for other indications. The labeling will make clear the indications approved under the LPAD pathway (see section VII., Conditions for Approval Under the LPAD Pathway).

A. Drug Intended to Treat a Serious or Life-Threatening Infection in a Limited Population of Patients With Unmet Needs

1. Treat a Serious or Life-Threatening Infection

To be eligible for approval via the LPAD pathway under section 506(h)(1) of the FD&C Act, a drug must be intended to treat a serious or life-threatening infection. FDA interprets the terms *serious* and *life threatening* in this provision to have the same meanings as they do under 21 CFR 312.300(b)(1) and 21 CFR 312.81(a), respectively. These definitions are described further in the

[7] Some drugs that are intended to treat a serious or life-threatening infection may not be *antibacterial or antifungal* drugs, in which case they would not be eligible for the LPAD pathway. See section 506(h)(1) of the FD&C Act. Sponsors with questions regarding whether a drug is considered an antibacterial or antifungal drug for purposes of LPAD pathway eligibility should contact the relevant review division or office in CDER or CBER, as applicable.

guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014) (Expedited Programs guidance).

FDA considers a drug to be intended to *treat* a serious or life-threatening disease or condition if the drug is intended to have an effect on a serious condition or a serious aspect of the serious or life-threatening condition, such as a direct effect on a serious manifestation or symptom of a condition or other intended effects.[8] This direct effect may include diagnosing, preventing, and/or treating a serious aspect of the condition. Accordingly, FDA intends to consider a drug to *treat a serious or life-threatening infection* if the drug diagnoses, prevents, or treats such an infection.

2. Limited Population

To be eligible for approval via the LPAD pathway under section 506(h)(1) of the FD&C Act, a drug must be intended for use in a limited population of patients. FDA interprets *limited population of patients* in this provision to mean a group of patients that is limited in a way that is clinically relevant to health care providers.[9] The labeling should define the limited population that the drug is intended to treat so that a health care provider would be able to identify the patients in the clinical setting for whom FDA determined the benefits of the drug outweigh its risks. A limited population may be a defined subset of a broader population of patients for whom the drug could potentially be effective or, in some cases, may be the only population of patients for whom the drug may be effective because of its narrow spectrum of activity.[10]

As noted above, FDA may consider certain drugs that prevent a serious or life-threatening infection to be eligible for approval under the LPAD pathway. For preventive drugs, FDA intends to evaluate the population of patients for which the drug is intended to be prescribed, not the expected incidence of the infection that the drug is intended to prevent, in determining whether the population is limited in a clinically relevant way, as described above. In general, FDA does not intend to consider a population to be limited in a way that is clinically relevant simply because a serious infectious disease that a drug is intended to prevent may occur infrequently or even rarely. For example, an antibacterial drug that would have a role in the preventive armamentarium for only a select patient population (e.g., mechanically ventilated patients) with no other options may be an appropriate candidate for the LPAD pathway; in contrast, an antibacterial drug intended for broad population-level prevention of an infrequently or rarely occurring serious or life-threatening disease generally would not be an appropriate candidate for the LPAD pathway.

3. Unmet Need

To be eligible for approval via the LPAD pathway under section 506(h)(1) of the FD&C Act, a drug must be intended for use by patients with unmet needs. FDA interprets the term *unmet need*

[8] This is consistent with the Expedited Programs guidance.

[9] The intended patient population does not need to be below a specific numerical threshold.

[10] See section V., Considerations for Approval of Drugs Under the LPAD Pathway, for illustrative examples.

in this provision to have the same meaning as the term *unmet medical need* in the Expedited Programs guidance.

The Unmet Medical Need guidance further explains the Agency's current thinking about unmet needs in patients who have serious bacterial diseases. The concepts described in the Unmet Medical Need guidance also apply to antifungal therapies for patients with unmet needs for serious fungal infections.

B. Standards for Approval Are Met

An applicant must provide in its application 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.[11] For additional information, see section V., Considerations for Approval of Drugs Under the LPAD Pathway.

The rules of construction set forth in section 506(h)(8) of the FD&C Act reiterate that the LPAD pathway provision does not alter FDA approval standards under the FD&C Act or the PHS Act, including the standards of evidence and applicable conditions for approval under these Acts. The provision also does not alter the authority of FDA to monitor drugs pursuant to these Acts.

IV. RELATIONSHIP TO OTHER PROGRAMS

An applicant seeking approval of a drug under the LPAD pathway is not precluded from seeking designation or approval under any other applicable provision in the FD&C Act or PHS Act for which the drug otherwise qualifies (e.g., fast track designation, breakthrough therapy designation, regenerative medicine advanced therapy designation, accelerated approval, priority review designation).[12] An applicant that seeks approval of a drug under the LPAD pathway may also seek designation, as applicable, under other programs, including qualified infectious disease product designation under the GAIN provisions[13] or orphan drug designation.[14]

[11] See sections 505(d)(1) and (5) of the FD&C Act. For a biological product to be licensed under section 351 of the PHS Act, a sponsor must demonstrate that its product is safe, pure, and potent. Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)).

[12] Section 506(h)(4) of the FD&C Act. Sponsors should consult the Expedited Programs guidance for generally applicable information about, the criteria for, and the benefits of FDA's expedited programs. See also the guidance for industry *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* (February 2019) for information about the regenerative medicine advanced therapy designation program and the application of other expedited programs to regenerative medicine therapies.

[13] Section 505E of the FD&C Act (21 U.S.C. 355f).

[14] Section 526 of the FD&C Act (21 U.S.C. 360bb).

V. CONSIDERATIONS FOR APPROVAL OF DRUGS UNDER THE LPAD PATHWAY

As discussed above, for an applicant to obtain approval of a drug under the LPAD pathway, the drug must meet the statutory standards for approval under section 505 of the FD&C Act or section 351 of the PHS Act, as applicable. The LPAD pathway requires that FDA's determination of safety and effectiveness take into account the severity, rarity, or prevalence of the infection a drug is intended to treat and the lack of alternative treatment in the limited population for which the drug is intended.[15] FDA may approve a drug under the LPAD pathway based upon a conclusion of a positive benefit-risk balance in the limited population, even though insufficient data exist to conclude that there is a favorable benefit-risk profile in a broader population.[16] As discussed in the Unmet Medical Need guidance, drugs with risks that would be unacceptable for a broad population may be acceptable for patient populations with serious diseases that do not have other treatment options. Acceptance of greater uncertainty or higher risk in patients with serious diseases and with unmet needs (such as those in the limited population targeted) is an appropriate approach to the benefit-risk assessment.[17] Compliance with the labeling and promotional material requirements in section 506(h)(3) can help the health care community understand that the drug was approved under a pathway in which benefits and risks were assessed in this manner.

The LPAD pathway should not be used to manage known or potential serious risks associated with a drug that may be addressed using other authorities under the FD&C Act or the PHS Act, if applicable.[18] The LPAD pathway should also not be used to salvage a trial that fails to demonstrate its objective (e.g., the LPAD pathway is generally not appropriate for submission of results of subpopulations from trials failing to meet their primary endpoint) or an inadequately designed development program.

If an applicant submits a request for approval of an application under the LPAD pathway, but the drug instead can be approved under the traditional approval pathway or the accelerated approval pathway alone, FDA will approve the application, but not under the LPAD pathway. For example, a drug for which the sponsor conducts a streamlined development program may be eligible for traditional approval if the clinical data support approval in a broader population.

When reviewing an application submitted under the LPAD pathway, FDA will take into account the severity, rarity, or prevalence of the infection that the drug is intended to treat and the

[15] See section 506(h)(2) of the FD&C Act.

[16] Ibid.

[17] See 21 CFR 312.80, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses. See also the Unmet Medical Need guidance.

[18] For example, see section 505-1 of the FD&C Act (21 U.S.C. 355-1).

availability or lack of alternative treatment for the limited population.[19] Required labeling statements help ensure that the health care providers understand the limited population of patients for whom the drug is intended and the limitations associated with streamlined development programs that will often support LPAD pathway approval (see section VII., Conditions for Approval Under the LPAD Pathway).[20] The conditions for approval under the LPAD pathway, including the labeling requirements, which can facilitate such health care provider understanding, will be taken into consideration by FDA in its benefit-risk assessment.

As discussed in section III., LPAD Pathway Defined, development programs for drugs eligible for approval under the LPAD pathway may follow the streamlined approaches described in the Unmet Medical Need guidance, such as the following:

- A clinical trial using noninferiority designs, including a single noninferiority trial at a body site of infection, which might include wider noninferiority margins than used in traditional development programs, or

- A superiority clinical trial in a limited population nested within a noninferiority clinical trial in a broader population.

A streamlined clinical development program for a limited population may involve smaller, shorter, or fewer clinical trials. In such circumstances, robust nonclinical evaluations (including animal models of infection) and pharmacokinetic/pharmacodynamic data may provide important information to help assess the benefits and risks of the drug in the intended limited population.[21]

Some examples of drugs for which approval under the LPAD pathway could be appropriate, assuming the statutory criteria are met, include the following: [22]

- An antibacterial drug with a narrow spectrum of activity (e.g., active against only a single species (or a few species) within a genus) intended to treat a limited patient population with a serious infection that is infrequently caused by the target pathogen or pathogens,[23] and

[19] Section 506(h)(2) of the FD&C Act. As discussed above, if a preventive drug's intended population is broad, FDA may not consider the drug to be intended to treat a limited population of patients, even if the infection occurs rarely.

[20] Section 506(h)(3)(A) of the FD&C Act.

[21] See the Unmet Medical Need guidance at page 4.

[22] Approved LPAD pathway drugs can be found on the FDA web page Limited Population Pathway for Antibacterial and Antifungal Drugs — the LPAD Pathway at https://www.fda.gov/drugs/development-resources/limited-population-pathway-antibacterial-and-antifungal-drugs-lpad-pathway.

[23] For further discussion regarding development of antibacterial drugs active against only a single species, see the Antimicrobial Drugs Advisory Committee meeting materials for April 13, 2017, available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-13-2017-meeting-antimicrobial-drugs-advisory-committee-meeting-announcement-04122017-04122017.

- An antibacterial or antifungal drug that, based on available therapy, would only have a role in the therapeutic armamentarium for a select patient population with limited or no other treatment options.[24]

The Unmet Medical Need guidance further explains FDA's current thinking about possible streamlined development programs and clinical trial designs for antibacterial drugs to treat serious bacterial diseases with unmet medical needs, including when patients have a serious bacterial disease for which effective antibacterial drugs are limited or lacking. The concepts described in the Unmet Medical Need guidance are applicable to drugs that are eligible for the LPAD pathway. Sponsors should consult the Unmet Medical Need guidance for further information about these potential development programs.

VI. PROCESS FOR THE LPAD PATHWAY

A. Advice

FDA anticipates that early and frequent communications between the Agency and sponsors interested in pursuing approval for their drugs under the LPAD pathway can help reduce overall drug development timelines. Pursuant to the requirement to provide prompt advice to sponsors of drugs seeking approval under the LPAD pathway,[25] FDA encourages sponsors to communicate with the Agency early in development regarding the planned development program.[26] Sponsors interested in the LPAD pathway should clearly state their intentions during discussions with FDA.

Depending on the proposed development program and available clinical data, FDA may be able to provide advice on potential eligibility for the LPAD pathway early in clinical development. However, results of the clinical trials intended to support approval of the application may change the Agency's conclusions about the benefits and risks of a drug and its eligibility for approval under the LPAD pathway. Furthermore, the approval of other drugs or other changes to available therapy may affect the Agency's determination of whether a drug addresses an unmet need. Accordingly, although FDA may provide advice on potential eligibility, FDA intends to make the determination of whether a drug meets the criteria for the LPAD pathway at the time of the drug's approval.

If a sponsor intends to request that a drug be approved under the LPAD pathway, FDA recommends that the sponsor include this request as a topic of discussion at the presubmission (pre-new drug application (pre-NDA) or pre-biologics license application (pre-BLA)) meeting.

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[24] For example, the drug product pretomanid tablets was approved under the LPAD pathway on August 14, 2019, for use in combination with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant or treatment-intolerant or nonresponsive multidrug-resistant tuberculosis. This patient population has unmet needs. See FDA's Drug Approval Package: Pretomanid web page at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212862Orig1s000TOC.cfm.

[25] Section 506(h)(6) of the FD&C Act.

[26] See the Unmet Medical Need guidance.

Following such discussion, if a sponsor seeks approval under the LPAD pathway, such a request must be made in writing with the NDA or BLA submission, as specified below.[27]

B. Written Request for Approval Under the LPAD Pathway

Section 506(h)(1)(C) of the FD&C Act requires a sponsor to submit a written request for FDA to approve a drug under the LPAD pathway. The applicant should submit the written request with the original NDA, BLA, or efficacy supplement, but FDA could accept the request at any time during the review of the application. If FDA concludes during its review of an application that the LPAD pathway would be appropriate for a drug and the applicant has not submitted a written request for approval under the LPAD pathway, FDA will communicate its recommendation to the applicant.

Written requests for approval under the LPAD pathway should contain the following information:

- Identification of the submission in the cover letter as "REQUEST FOR LPAD APPROVAL";
- The specific serious or life-threatening infection that the drug is intended to treat; if multiple indications are sought, specify which indications are proposed for approval under the LPAD pathway;
- The limited population of patients with unmet needs for whom the drug is intended; and
- A concise summary of how the conditions of approval under the LPAD pathway (see section VII., Conditions of Approval Under the LPAD Pathway) affect the benefit-risk assessment of the drug.

VII. CONDITIONS OF APPROVAL UNDER THE LPAD PATHWAY

A. Labeling

Drugs approved under the LPAD pathway are required under section 506(h)(3)(A) of the FD&C Act to include certain labeling statements to convey to the health care community[28] that the drug has been shown to be safe and effective for use only in a limited population. To make fully informed decisions, the health care community should understand that approval of a drug under the LPAD pathway was based on a benefit-risk assessment that more flexibly accounted for the severity, rarity, or prevalence of the infection the drug is intended to treat and the lack of alternatives available for the patient population.

[27] Section 506(h)(1)(C) of the FD&C Act.

[28] For purposes of this guidance, the term *health care community* includes health care providers and patients and their families or caregivers.

Section 506(h)(3)(A)(i) of the FD&C Act requires all labeling and advertising of a drug approved under the LPAD pathway to contain the statement "Limited Population" in a prominent manner and adjacent to, but not more prominent than, the proprietary name of such drug, if any, or, if there is no proprietary name, the established name of the drug product as defined in section 502(e)(3) of the FD&C Act (21 U.S.C. 352) or, in the case of a biologic product, the proper name. In most cases, to fulfill the prominence requirement, the font size, typeface, case, and bolding should match that of the adjacent proprietary name (or nonproprietary name if there is no proprietary name).

Section 506(h)(3)(A)(ii) of the FD&C Act requires the prescribing information of drugs approved under the LPAD pathway to include the statement: "This drug is indicated for use in a limited and specific population of patients."

Below are further recommendations about the "Limited Population" statements and the requirements for specific types of labeling.

If approval under the LPAD pathway is sought for fewer than all indications when multiple indications are approved or proposed, we recommend that applicants consult the review division for advice regarding how to incorporate LPAD pathway-related information into labeling.

1. Carton Labeling and Immediate Container Label

The statement "Limited Population" should be included on the principal display panel of the product carton(s) and, if space permits,[29] immediate containers, adjacent to the proprietary name (or nonproprietary name if there is no proprietary name) in a manner that is consistent with the requirements outlined above. In cases where the product is available as a dosage form with only a container label (no carton labeling), the "Limited Population" statement should be included on the principal display panel of the container label, adjacent to the proprietary name (or nonproprietary name if there is no proprietary name). To provide clarity, FDA recommends including an asterisk next to the "Limited Population" statement with a footnote at the bottom of the principal display panel,[30] stating: "See prescribing information for [drug name] for information about the limited population."[31]

2. Prescribing Information

a. Highlights of Prescribing Information

In the Highlights of Prescribing Information (Highlights), on the line immediately beneath the statement "Initial U.S. Approval," the statement "**LIMITED POPULATION**" should appear in uppercase letters and bold print.

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[29] See 21 CFR 210.10(i) for additional information about packaging that is too small for the additional statements.

[30] This could also be on a side panel if space limitations preclude placement on the principal display panel.

[31] If the drug is approved for multiple indications, some of which are approved under the LPAD pathway and some are not, the language could instead read: "See prescribing information for [drug name] for information about the indicated populations."

Under the INDICATIONS AND USAGE heading in the Highlights, the statement "Limited Population" should be included in the same font size, typeface, and case as the proprietary name (or nonproprietary name if there is no proprietary name) before each indication approved under the LPAD pathway.

Drugs approved under the LPAD pathway must include the following statement in the prescribing information: "This drug is indicated for use in a limited and specific population of patients."[32] In the Highlights, FDA recommends that this statement be included at the end of each indication approved under the LPAD pathway. If all indications for a drug were approved under the LPAD pathway, the statement "This drug is indicated for use in a limited and specific population of patients" can be a standalone bullet point preceding the indications instead of being repeated in each indication. In the Highlights, indications for drugs approved under the LPAD pathway should also convey the patient population for which the drug is approved (e.g., the patient population with a serious infection caused by a bacterial or fungal pathogen for which the patient has limited therapeutic options) as discussed in the Unmet Medical Need guidance. For example:

- LIMITED POPULATION: MYDRUG is a (established pharmacologic class) indicated, in adults who have limited or no alternative treatment options, for the treatment of Disease-Y caused by designated susceptible microorganisms. This drug is indicated for use in a limited and specific population of patients. (1.x)

b. Full Prescribing Information

In the INDICATIONS AND USAGE section in the Full Prescribing Information, the statement "Limited Population" should be included in the same font size, typeface, and case as the proprietary name (or nonproprietary name if there is no proprietary name) before each indication approved under the LPAD pathway.

Labeling for drugs approved under the LPAD pathway must include the following statement: "This drug is indicated for use in a limited and specific population of patients."[33] In the Full Prescribing Information, FDA recommends that this statement be included in the INDICATIONS AND USAGE section at the end of each indication approved under the LPAD pathway. For drugs approved under the LPAD pathway, the indication should also convey the population of patients for whom the drug is approved (e.g., the population of patients who have a serious infection caused by a bacterial or fungal pathogen for which the patient has limited therapeutic options) and may summarize the limitations of the available data that supported the approval. For example:[34]

[32] Section 506(h)(3)(A)(ii) of the FD&C Act.

[33] Section 506(h)(3)(A)(ii) of the FD&C Act.

[34] This is an example and the language may be adjusted or changed as necessary.

- LIMITED POPULATION: MYDRUG is indicated in adults who have limited or no alternative treatment options for the treatment of Disease-Y caused by the following susceptible gram-negative microorganisms: *[Genus species #1, Genus species #2, etc.]*. Approval of this indication is based on limited clinical safety and effectiveness data. This drug is indicated for use in a limited and specific population of patients.

3. Patient Labeling

If FDA-approved patient labeling is required or recommended for the drug, the statement "Limited Population" should be included before the proprietary name in the drug title (or nonproprietary name if there is no proprietary name) of the patient package insert, Instructions for Use, and/or Medication Guide. The font size, typeface, case, and bolding of "Limited Population" should match that of the adjacent proprietary name (or nonproprietary name if there is no proprietary name). FDA recommends including an asterisk next to the "Limited Population" statement that corresponds to the statement explained below.

For example: **LIMITED POPULATION*: MYDRUG (mye-drug)**

*[DrugName] was approved by FDA using the Limited Population pathway. FDA has approved this drug for a limited and specific population of patients that have few or no other options.

B. Promotional Material

Under section 506(h)(3)(B) of the FD&C Act, an applicant of a drug approved under the LPAD pathway must submit copies of all promotional materials related to the LPAD pathway drug at least 30 calendar days before dissemination of materials (predissemination). In addition, section 506(h)(3)(A)(i) requires promotional materials, including promotional labeling and advertising, to include the statement "Limited Population" in a prominent manner and adjacent to, but not more prominent than, the proprietary name of such drug, if any, or if there is no proprietary name, the established name of the drug product as defined in section 502(e)(3) of the FD&C Act (21 U.S.C. 352) or, in the case of a biologic product, the proper name. The applicant of a drug approved under the LPAD pathway must also ensure that promotional materials are truthful and nonmisleading, as required under the FD&C Act and FDA's implementing regulations.[35]

Applicants may apply the recommendations in section VII.A., Labeling, to their promotional materials.

The following procedural outline is designed to assist applicants in satisfying the 30-calendar-day predissemination requirement. These procedures are, in part, adapted from the Agency's guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic*

[35] See, e.g., sections 201(n), 502(a), and 502(n) of the FD&C Act and 21 CFR 1.21 and 202.1(e)(5). The Office of Prescription Drug Promotion within CDER or the Advertising and Promotional Labeling Branch in CBER is the primary office dedicated to the review and enforcement of these requirements.

Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs (June 2019) (e-Sub guidance).[36]

Applicants should do the following to meet the predissemination requirement for LPAD pathway drugs:

- Prepare draft promotional materials and submit those materials to the Agency as described in the e-Sub guidance section IV.C. Applicants should review section IV.C. of the e-Sub guidance for accompanying information for the submission. Applicants should also note on their accompanying correspondence to the Office of Prescription Drug Promotion in the Center for Drug Evaluation and Research that the submission is for a "Pre-Submission of Promotional Materials for a Limited Population Pathway Antibacterial or Antifungal Drug."

- Upon receipt of a complete submission by the Agency, the 30-calendar-day predissemination *clock* will begin. This is *calendar day 1*. After 30 calendar days, or *calendar day 31*, the statutory predissemination requirement will be satisfied.

While the above procedure satisfies an applicant's statutory obligation at section 506(h)(3)(B) of the FD&C Act, applicants must still comply with all other statutory and regulatory requirements for promotional materials, including that their materials be truthful and nonmisleading. Furthermore, applicants must comply with the postmarketing requirements under the FD&C Act and implementing regulations, which require that all prescription drug product applicants submit labeling or advertising devised for promotion of the drug product at the time of initial dissemination or publication (21 CFR 314.81(b)(3)(i) and 21 CFR 601.12(f)(4)).[37]

C. Termination of Limitations

Under section 506(h)(7) of the FD&C Act, FDA may terminate the limitations associated with an LPAD pathway approval for an individual drug or indication upon approval of a subsequent supplement, when FDA has determined that clinical data demonstrate that the drug is safe and effective for a broader indication.[38] Additional clinical data should enable FDA to conclude that the labeling and other conditions of the LPAD pathway approval are no longer necessary for the drug product.[39] When determining whether limitations should be terminated for a drug approved under the LPAD pathway, FDA intends to consider any differences regarding the indicated patient populations; conditions of use; and dosage, duration, and strength between the proposed broader indication and the indication approved under the LPAD pathway. FDA encourages

[36] For more information, see the e-Sub guidance.

[37] For information related to fulfilling the postmarketing requirement for promotional materials, see the e-Sub guidance at section IV.A.

[38] Postmarketing studies are not required under the LPAD pathway. An applicant can choose to pursue a broader indication, if warranted, for a drug or indication approved under the LPAD pathway.

[39] Section 506(h)(7) of the FD&C Act.

applicants to discuss with the Agency the design of clinical trials and types of evidence intended to support termination of LPAD pathway limitations.

An applicant submitting an efficacy supplement to support termination of LPAD pathway limitations should identify the submission in the cover letter as "REQUEST FOR TERMINATION OF LPAD PATHWAY LIMITATIONS." If LPAD pathway limitations are terminated, FDA will indicate the termination in the approval letter. Upon approval, the LPAD pathway language will be removed from the labeling (e.g., the statement "Limited Population" will be removed from all the approved labeling and the sentence "This drug is indicated for use in a limited and specific population of patients" will be removed from the INDICATIONS AND USAGE section). Upon approval of such a supplement, the presubmission of promotional materials under section 506(h)(3)(B) of the FD&C Act will no longer be required.