Limited Population Pathway for Antibacterial and Antifungal Drugs

Guidance for Industry

DRAFT GUIDANCE

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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)

June 2018
Procedural

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

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff 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 in the development of certain new antibacterial and antifungal drugs for approval under the LPAD pathway. This guidance also is intended to assist sponsors[4] in developing labeling, including prescribing information, patient labeling, and carton/container labeling, that incorporates certain statements required by section 506(h).

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

[1] This guidance has been prepared by the Office of Antimicrobial Products 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*, or *products* include both human drugs and biological products regulated by CDER and CBER unless otherwise specified.

[4] For purposes of this guidance, the term *sponsor* includes any sponsor of an 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.

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 guidance for industry *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases* (Unmet Medical Need guidance),[5] 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 (FDASIA), 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.

III. LPAD PATHWAY DEFINED

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

- 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).

See section 506(h)(1) of the FD&C Act. As discussed in greater detail in section V., Considerations for Approval of Drugs Under the LPAD Pathway, development programs for

[5] 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/RegulatoryInformation/Guidances/default.htm.

[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.

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.

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

A. The Drug Is 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 disease or condition. FDA interprets *serious disease or condition* 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 guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (Expedited Programs guidance).

Consistent with the 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. 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 such a way that is clinically relevant to health care providers. 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.[7]

As noted above, FDA may consider certain products that prevent a serious and life-threatening infection to be eligible for approval under the LPAD pathway. For preventative products, FDA intends to evaluate the population of patients for which the drug is intended, 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. FDA would not consider a

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

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.

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* in this provision to have the same meaning as *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 an unmet need for serious fungal infections.

B. The Standards for Approval Are Met

A sponsor 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.[8]

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

Sponsors seeking approval of a drug under the LPAD pathway are 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).[9] A sponsor who seeks approval of a drug under the LPAD pathway may

[8] 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)).

[9] 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 draft guidance for industry *Expedited Programs for Regenerative Medicine Therapies for Serious Conditions* for information about the regenerative medicine advanced therapy designation program and the application of other expedited programs to regenerative medicine therapies. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

also seek designation, as applicable, for other programs, including qualified infectious disease product designation under the GAIN provisions[10] or orphan drug designation.[11]

V. CONSIDERATIONS FOR APPROVAL OF DRUGS UNDER THE LPAD PATHWAY

As discussed above, for a sponsor 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 PHS Act, as applicable. The LPAD pathway requires FDA to take into account in its determination of safety and effectiveness the severity, rarity, or prevalence of the infection a drug is intended to treat and the lack of alternative treatment in the limited population a drug is intended for (see section 506(h)(2)). FDA may approve such drug although not enough data exists to conclude that there is a favorable benefit-risk profile in a broader population. 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 an unmet need is an appropriate approach to the benefit-risk assessment.[12] 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 are 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.[13] The LPAD pathway should also not be used to salvage a trial that fails to demonstrate its objective or an inadequately designed development program. The Agency does not consider the LPAD pathway to be appropriate for products that could instead meet the criteria for non-LPAD pathway approval.

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 availability or lack of alternative treatment for the limited population.[14] Required labeling statements help ensure that the health care provider understands the limited population of

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

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

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

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

[14] 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.

patients for whom the drug is intended and the limitations surrounding an LPAD pathway approval (see section VII., Conditions for Approval Under the LPAS Pathway).[15]

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:

- Clinical trials using noninferiority designs, including a single noninferiority trial at a body site of infection or trial designs with wider noninferiority margins than used in traditional development programs

- Nested noninferiority/superiority clinical trials

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 (exposure-response) data may provide important supportive information to help assess the benefits and risks of the drug in the intended limited population.

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

- An antibacterial drug with a narrow spectrum of activity (e.g., active against only a single species (or a few species) within a genus), and the target pathogen or pathogens occur infrequently at any body site of infection.[16]

- 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 no other options.

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.

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

[16] See the Antimicrobial Drugs Advisory Committee meeting materials for April 13, 2017, available at https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm551361.htm.

VI. PROCESS FOR THE LPAD PATHWAY

A. Advice

FDA anticipates that early and frequent communications between the Agency and sponsors interested in pursuing approval under the LPAD pathway for their products can help reduce overall product development timelines. Pursuant to the requirement to provide prompt advice to sponsors of drugs seeking approval under the LPAD pathway,[17] FDA encourages these sponsors to communicate with the Agency early in development regarding the planned development program.[18] 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 a sponsor 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. 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.[19]

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 sponsor ordinarily 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.

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"

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

[18] See the Unmet Medical Need guidance.

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

- The specific serious or life-threatening infection that the drug is intended to treat

- The limited population of patients with unmet needs for whom the drug is intended

- 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[20] that the drug has been shown to be safe and effective only for use 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 took 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.

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, and not more prominent than, the proprietary name of such drug, if any, or if there is no proprietary name, the established name as defined in section 503(e)(3) of the FD&C Act (21 U.S.C. 353), 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.

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" statement and the requirements for specific types of 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,[21] immediate containers, adjacent to the proprietary name or nonproprietary 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

[20] The term *health care community* here includes health care providers, patients, and their families or caregivers.

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

the container label, adjacent to the proprietary name or nonproprietary 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 stating "See the full prescribing information for [drug name] for information about the limited population."

2. Prescribing Information

a. Highlights of Prescribing Information

On the line immediately beneath the statement "Initial U.S. Approval," the statement "**LIMITED POPULATION**" should appear in uppercase letters and bold print.

Under the INDICATIONS AND USAGE section heading in 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 that received LPAD pathway approval.

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."[22] In 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 included in each indication. The Highlights indications statement for drugs approved under the LPAD pathway should also reflect the patient population for which the drug is approved (e.g., the patient population with a serious infection caused by a bacterial 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. As only limited clinical safety and effectiveness data for MYDRUG are currently available, reserve MYDRUG for use in adults who have limited or no alternative treatment options. 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, 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.

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

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."[23] In the full prescribing information, FDA recommends that this information 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 INDICATIONS AND USAGE section should also reflect 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 pathogen for which the patient has limited therapeutic options) and summarize the limitations of the available data that supported the approval, as discussed in the Unmet Medical Need guidance. For example:

- 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.]*. As only limited clinical safety and effectiveness data for MYDRUG are currently available, reserve MYDRUG for use in adults who have limited or no alternative treatment options. Approval of this indication is based on *[summarize the limitations of available data that supported the approval]*. This drug is indicated for use in a limited and specific population of patients.

3. Patient Labeling

If patient labeling is appropriate for the drug, "Limited Population" should be included after the pronunciation/phonetic spelling of the proprietary name in the product title (or nonproprietary name if the product does not have a 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).

For example: MYDRUG (maj drəg) LIMITED POPULATION.

If patient labeling is appropriate for the drug, FDA suggests including the following statement:

> This product was approved by FDA using the Limited Population pathway. This means FDA has approved this drug for a limited and specific patient population, and studies on the drug may have only answered focused questions about its safety and effectiveness.

B. Promotional Material

Under section 506(h)(3)(B) of the FD&C Act, a sponsor of a drug approved under the LPAD pathway must submit copies of all promotional materials related to the product at least 30 calendar days before dissemination of materials. The Agency intends to review these materials to ensure they adequately display the statements required to be included in labeling for drugs approved under this pathway and that the labeling otherwise accurately conveys the limited population for which the drug is indicated and for the drug's benefits and risks.

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

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 product upon approval of a subsequent supplement, when FDA has determined that clinical data demonstrate that the product is safe and effective for a broader indication. The 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.[24] 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 indication and the indication approved under the LPAD pathway.

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