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Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers

Guidance for Industry

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

June 2025
Clinical/Antimicrobial

Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers

Guidance for Industry

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10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
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Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers 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 is intended to assist sponsors in the clinical development of new antibacterial drugs to treat serious bacterial diseases, particularly those caused by antimicrobial drug-resistant organisms, in patients with unmet medical need.[2] For example, antibacterial drugs that are active against only a single species or few species within a genus of bacteria can be developed for the treatment of serious bacterial diseases[3] in patients with an unmet medical need.[4] For new antibacterial drugs that treat serious bacterial diseases with a potential to address an unmet medical need, a more flexible development program may be acceptable to facilitate development.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) provides authority for several regulatory programs that are intended to expedite development and review of drugs for serious conditions. For example, section 506(h) of the FD&C Act provides a limited population pathway

[1] This guidance has been prepared by the Division of Anti-Infectives in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products regulated in CDER unless otherwise specified.

[3] 21 CFR 312.300(b) defines "a [s]erious disease or condition" to mean "a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one."

[4] For a detailed discussion of regulatory programs intended to expedite development and review of drugs (e.g., fast track, breakthrough) and their attendant criteria and definitions, see the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

for approval of antibacterial and antifungal drugs (LPAD), if the drugs are intended to treat a serious or life-threatening infection in a limited population of patients with unmet medical needs.[5] In 2020, the Agency issued guidance on the implementation of section 506(h) of the FD&C Act..[6] Sponsors are encouraged to discuss proposed approaches with the Agency.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively. In addition, although there is some overlap with the concepts discussed in the above-referenced guidance for industry *Limited Population Pathway for Antibacterial and Antifungal Drugs* (August 2020), the present guidance is limited to antibacterial drug development and addresses aspects of drug development that may not necessarily fall within the scope of the August 2020 guidance on the LPAD pathway.[7]

This guidance finalizes the draft guidance for industry *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases (Revision 1)* (May 2022).[8]

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

Antibacterial drug resistance continues to be a public health concern. It has led to an increasing number of patients with serious bacterial diseases, such as hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, complicated intra-abdominal infections, and complicated urinary tract infections, which may not respond to currently available antibacterial drugs. Additional areas of unmet need may include serious bacterial infections whose treatment is not addressed adequately by available therapy.

[5] Section 506(h) was added to the Federal Food, Drug, and Cosmetic Act (FD&C Act) by section 3042 of the 21st Century Cures Act (Public. Law 114-255) (2016).

[6] See the guidance for industry *Limited Population Pathway for Antibacterial and Antifungal Drugs* (August 2020).

[7] The August 2020 guidance is intended to assist sponsors in the development of certain new antibacterial and antifungal drugs for approval under the LPAD pathway by describing criteria, processes, and other general considerations for demonstrating the safety and effectiveness of limited population antibacterial and antifungal drugs.

[8] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Conducting clinical trials to evaluate antibacterial drugs for the treatment of subjects with a serious bacterial disease can be challenging for a number of reasons, including (1) the need to promptly initiate empiric antibacterial therapy to reduce the risk of morbidity and mortality; (2) the severity of the acute illness in subjects (e.g., delirium in the setting of acute infection), which could make some trial enrollment procedures challenging ; (3) the diagnostic uncertainty with respect to the etiology of the subjects' underlying disease, including the specific bacterial etiology; and (4) the potential need for concomitant antibacterial drug therapy (often empiric) with a spectrum of activity that may overlap with the activity of the antibacterial drug being studied, which can make assessment of the efficacy of the investigational drug difficult.

Given the urgent need for development of new antibacterial drugs to treat serious bacterial diseases, FDA intends to apply appropriate regulatory flexibility with regard to meeting the requirements for substantial evidence of effectiveness in such situations, as stated in 21 CFR part 312, subpart E (Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses):

> *The Food and Drug Administration (FDA) has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated.*[9]

The Questions and Answers section below expands on the ways in which the Agency may exercise this flexibility.

III. QUESTIONS AND ANSWERS

The following questions and answers are provided to explain the FDA's current thinking on flexible development programs that may be appropriate for development of antibacterial drugs to treat serious bacterial diseases in patients with an unmet medical need.

1. What types of antibacterial drugs may be appropriate for a more flexible development program?

Candidates for a flexible development program are antibacterial drugs intended to treat serious bacterial infections in patients who have few or no available treatments.[10] Antibacterial drugs that offer an efficacy advantage over available treatments for serious bacterial infections may be eligible, as may antibacterial drugs that offer a safety advantage over existing treatments for serious bacterial infections, if efficacy in that unmet need patient population has been

[9] 21 CFR 312.80.

[10] For a more general discussion of the concepts of *unmet medical need* and *serious conditions*, see the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

established. Such drugs may have: (1) a new mechanism of action that preserves antibacterial activity against bacteria that have mechanisms of resistance to other available antibacterial drugs, (2) an added inhibitor that neutralizes a mechanism of resistance, (3) an alteration in the structure of the molecule that makes the drug no longer susceptible to the mechanisms of resistance to existing drugs, or (4) some other characteristic that has a potential to lead to enhanced effectiveness. A drug that has slightly greater potency (e.g., more active by 2- to 3-fold dilutions based on in vitro testing) generally would not be considered a drug that addresses an unmet medical need.

2. Can a drug that treats a single species of bacteria be a candidate for a flexible development program?

Yes, a drug that treats a single species (or a few species) of bacteria that causes serious disease can be a candidate for a flexible development program. For an antibacterial drug active against only a single species (or few species) within a genus, possible clinical trial design recommendations are discussed below. When planning for such a drug development program, sponsors should consider the following factors for clinical trials:

- The frequency with which the bacterial species of interest causes serious infections
- The use and availability of rapid diagnostic tests to promptly identify subjects with the bacterial etiology of interest as the cause of their infection
- The codevelopment of a rapid diagnostic test for use in clinical practice[11]

3. What are important nonclinical considerations in a flexible development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and an unmet medical need?

A sponsor developing a drug using a flexible clinical development program must still provide adequate data to demonstrate that the drug is safe and effective to meet the statutory standards for approval.[12] Sponsors should evaluate the antibacterial activity of the new drug, mechanism of action, mechanism(s) of resistance, mutation frequency, and whether the new drug is affected by mechanisms that confer resistance to other drugs and its potential as a candidate for the treatment of patients with serious infections and few or no treatment options.

[11] The Center for Devices and Radiological Health regulates devices for the purpose of use in the clinical care of patients. Sponsors should discuss with the FDA whether an investigational in vitro diagnostic device is intended to be used with a corresponding drug as a companion diagnostic device. See the guidances for industry and FDA staff *In Vitro Companion Diagnostic Devices* (August 2014) and *Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices* (February 2019).

[12] See section 505(d) of the FD&C Act.

To the extent that a flexible clinical development program involves smaller or fewer clinical trials, it is likely that less safety data will be generated, and the nonclinical studies may assume an even more important role in contributing to the evaluation of the safety of an antibacterial drug. Thus, the nonclinical evaluations generally should not be abbreviated.[13] In certain circumstances, flexibility on the timing of certain nonclinical studies (e.g., carcinogenicity, reproductive toxicology studies, etc.) to support ongoing clinical development may be considered. Sponsors are encouraged to discuss their nonclinical safety program with the Agency early in the development process.

The nonclinical data package should provide information about the investigational drug, including the following:

- In vitro activity of the investigational drug, including the minimum inhibitory concentration (MIC) from a representative sample of target bacterial pathogens[14]
- Activity in appropriate animal models of infection[15]
- Evidence for the antibacterial drug's ability to achieve appropriate concentrations in relevant tissue sites from nonclinical studies (e.g., from appropriate animal models of infection)
- The mechanism of action and whether mechanisms of resistance to other drugs affect its antibacterial activity
- The evaluation of pharmacokinetic/pharmacodynamic (PK/PD) relationships from nonclinical models of infection, such as the PK/PD index that is associated with activity in relevant in vivo models and/or in vitro models based on (1) the area under the unbound plasma concentration time curve over the MIC, (2) maximum unbound plasma concentration over the MIC, (3) time above the MIC, or (4) other appropriate metrics
- The target value of the PK/PD index that is associated with activity in the animal model

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[13] Other guidances for industry discuss the important elements of the nonclinical safety evaluation. See, for example, the ICH guidances for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010), *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (May 2012), and *S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* (October 2005), and the guidances for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products* (November 1995) and *INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information* (May 2003).

[14] See the guidance for industry *Microbiology Data for Systemic Antibacterial Drugs — Development, Analysis, and Presentation* (February 2018).

[15] We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

- Dose and frequency of administration that are evaluated in relevant in vivo and/or in vitro models of infection based on PK parameters obtained from human PK studies

4. What are clinical trial design considerations in a more flexible development program?

Different approaches can be used to evaluate an antibacterial drug for the treatment of a serious bacterial disease in patients with an unmet medical need. The approaches outlined below are provided as examples that sponsors may consider using. These approaches are not all inclusive, and some approaches may be used together. As the therapeutic armamentarium and the unmet medical need for serious bacterial diseases are continuously evolving, sponsors are encouraged to discuss their development plans early with the Agency. The following are examples of trial design considerations.

a. Noninferiority clinical trials

For serious bacterial diseases for which there are existing effective treatment options, but unmet need still exists (e.g., for patients intolerant to existing therapies), efficacy of an investigational drug can be established in a noninferiority trial.[16] The active comparator regimen used in the trial should provide the best available therapy for the population enrolled in the clinical trial. The clinical trial population should include subjects with illness severity and comorbid conditions that reflect the patient population with unmet medical need to ensure the generalizability of a finding of safety and efficacy. A randomized trial design is needed because both comparative safety and efficacy evaluations can be performed. The randomized clinical trial data can be supported by confirmatory evidence from nonclinical studies and other sources demonstrating the activity of the investigational drug against resistant phenotypes. The sources and extent of confirmatory evidence that the sponsor proposes to use should be discussed with FDA early in development.[17]

Given that the antibacterial drug would be indicated for use only in patients who have limited treatment options, the characterization of efficacy in a noninferiority trial could be based on a larger noninferiority margin than is typically recommended in the disease-specific guidances, but acceptance of the noninferiority margin would depend on the type and degree of unmet need. Under these circumstances, a drug meeting the margin would still be considered effective compared with a hypothetical placebo but would retain less than the usual fraction of the efficacy

[16] The existence of treatment options may not preclude using a flexible development program; please refer to comments under Question 15 for further discussion.

[17] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023). When final, this guidance will represent the FDA's current thinking on this topic.

of the comparator.[18] The primary analysis of noninferiority should exclude subjects with baseline pathogens resistant to the control drug.[19]

As new treatment options have become available, it is now possible to enroll subjects with infections caused by certain antibacterial drug-resistant phenotypes of interest that would be susceptible to both the active comparator and the study drug.

b. Superiority clinical trials

An investigational drug can be compared with best available active control therapy in a single randomized controlled superiority trial. Further, in general, meeting the "substantial evidence of effectiveness" standard with a single clinical trial will also necessitate additional confirmatory evidence. Sponsors should discuss with FDA the type of trial design—for example, a trial enrolling subjects who have a particular type of infection (e.g., ventilator-associated bacterial pneumonia) or who have more than one type of infection of similar severity (e.g., ventilator-associated bacterial pneumonia and bloodstream infections)—and inferential statistical evaluations for a finding of superiority.

A typical criterion for concluding that a superiority trial is positive (showed an effect) is a p value of <0.05 (two sided). A lower p value, for example, would often be expected for reliance on a single trial. For a serious bacterial disease with no available therapy or a rare disease where sample size might be limited, a somewhat higher p value—if prespecified and appropriately justified—might be acceptable.

Substantial evidence of effectiveness of an investigational drug may also be demonstrated in an add-on placebo-controlled superiority trial design in which all subjects also receive standard or best available treatment.

5. Can serious infections at different body sites be studied in the same clinical trial?

Yes; however, there are potential challenges with studying serious infections at different body sites in the same trial (e.g., a trial enrolling patients with complicated intra-abdominal infections and also enrolling other patients with complicated urinary tract infections). Considerations may include (a) stratified enrollment or other approaches to ensure that similar proportions of subjects with different serious infections are enrolled in each study arm and that numbers of subjects are sufficient to enable analysis of efficacy in each infection, (b) determination of the primary efficacy endpoint and planned statistical analysis, (c) similar disease severity and causative pathogens among the infections studied, and (d) labeling implications for inclusion of serious infections at different body sites in the same trial (discussed further in the response to Question 16). Sponsors are encouraged to discuss with FDA early in development their plans for studying serious infections at different body sites in the same trial.

[18] See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

[19] A hierarchical nested noninferiority/superiority analysis can be considered if a sufficient number of subjects with infection caused by bacteria resistant to the control drug are expected to be enrolled in the trial.

6. What are examples of statistical approaches or randomization strategies in a flexible clinical program?

To the extent possible, trials should be double-blinded. If there is a compelling reason for single-blind or open-label trial designs, sponsors should discuss with the Agency efforts to minimize bias before initiating the trial.

Group sequential designs can be useful and flexible for early stopping based on efficacy or futility. Adaptive design clinical trials or trial designs with features such as those discussed below can be considered.[20]

A cluster randomization strategy is one possible approach that could be explored. With appropriate informed consent procedures, cluster randomization may facilitate trial enrollment. Subjects enrolled at sites randomized to the standard-of-care arm would be treated consistent with the predefined standard of care at that site, while subjects enrolled at sites randomized to the investigational drug arm would be treated with the investigational drug. This strategy is best suited for trials with a large number of clinical centers, each enrolling a relatively small number of subjects. With adequate numbers of clinical centers, randomization should ensure balance between the treatment groups with respect to both site and subject-level characteristics.

Clinical trial networks also might simplify trial conduct and enhance feasibility for evaluating new antibacterial drugs. Innovative clinical trial approaches such as platform or umbrella trials are also possibilities that could be considered.[21]

Factorial designs are another consideration. Clinical trials are often conducted in intensive care units to evaluate interventions whose mechanisms of action differ from antibacterial drugs (e.g., anti-inflammatory therapies). A factorial design would simultaneously randomize subjects in such a trial to one of two different antibacterial drug regimens and one of two different nonantibacterial interventions, and thus allow the single trial to answer two questions. Sponsors interested in using a factorial design should discuss with the FDA whether any interactions are expected between the antibacterial and nonantibacterial interventions.

7. What is the importance of PK/PD (exposure-response) data in a more flexible development program?

Information on the distribution of MICs for the relevant bacteria based on recent surveillance data, the results of PK/PD (exposure-response) assessments in animal models, and results from human PK trials should be integrated to help identify the appropriate dose and frequency of

[20] Clinical trial designs with adaptive features may enhance the efficiency of the trial; sponsors who are considering an adaptive design are encouraged to consult the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (December 2019).

[21] See the draft guidance for industry *Master Protocols for Drug and Biological Product Development* (December 2023). When final, this guidance will represent the FDA's current thinking on this topic.

administration for evaluation in clinical trials.[22] In some previously conducted clinical trials, wider variability in exposure was observed in subjects who were seriously ill compared with those who were less seriously ill. Additionally, increased variability in exposure has also been noted by the type of infection (e.g., ventilator-associated bacterial pneumonia). Thus, it is important that adequate evaluation of the PK and dose justification be provided for patients with an unmet medical need who have the infection type to be evaluated. PK information from humans should include information about the distribution of the drug to the site of action (e.g., epithelial lining fluid). Although it is ideal to evaluate drug penetration to the site of action in the intended patient population, given the challenges of conducting such a study in subjects, the information on drug penetration to the site of action can be obtained in healthy subjects. Comparison of human and animal exposure data should include correction for any differences in plasma protein binding and distribution to the site of action.

Collection of PK data in clinical trials (e.g., sparse sampling in all subjects enrolled in clinical trials) may help address potential questions about efficacy or safety that arise and help describe the effects of intrinsic and extrinsic factors on pharmacokinetics and pharmacodynamics. Patients with serious bacterial diseases with an unmet medical need often have important comorbidities, notably renal or hepatic impairment, and, therefore, an increased likelihood of alterations in PK. An important consideration in drug development is to characterize PK in such subjects. For example, understanding the PK of the investigational drug in subjects with renal or hepatic impairment early in development could facilitate enrollment of such subjects in clinical trials (e.g., by providing guidance on dosing).

8. What is the size of the premarketing safety database in a flexible development program?

The premarketing safety database of an investigational drug should be adequate in light of its potential benefit. In general, a safety database for a drug that is the subject of a more flexible development program should include approximately 300 subjects at the dose and duration of therapy proposed for marketing. This safety database could include subjects from all phases of clinical development and include subjects who do not have an unmet medical need.

9. What other safety regulatory requirements should be considered in a flexible development program?

Section 901 of the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85) created sections 505(o) and 505-1 of the FD&C Act. Section 505(o)(3) of the FD&C Act authorizes the FDA to require certain postmarketing studies and clinical trials for prescription drugs.[23] Section 505-1 authorizes the FDA to require a risk evaluation and mitigation strategy

[22] See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* (April 2003) and the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration* (November 1994).

[23] For further information on the FDA's current thinking on this topic, see the draft guidance for industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019). When final, this guidance will represent the FDA's current thinking on this topic.

(REMS) if the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug.[24]

As described earlier, a more flexible development program may include a relatively small safety database. In some instances, this may lead to uncertainties about findings of a potential serious risk (e.g., strength of the association of the risk with drug treatment, the rate of occurrence of the risk). In these cases, when the approval standard has been met, the FDA may determine that a postmarketing study or clinical trial is needed to further characterize the risk.

10. Will the FDA accept greater toxicity for drugs that treat patients with a serious bacterial disease and an unmet medical need?

The safety of a drug is assessed by weighing its risks against its benefits. Drugs with risks that would be unacceptable for a broad population may be acceptable for patients with a serious bacterial disease who do not have other treatment options. As stated previously, acceptance of greater uncertainty or higher risk in patients with a serious bacterial disease and an unmet medical need is an appropriate approach to the risk-benefit assessment.[25]

11. Does a more flexible development program for antibacterial drugs result in a lower regulatory standard for drug approval?

No. Drugs approved on the basis of a more flexible development program must, among other things, meet the statutory standards for safety and effectiveness set forth in section 505(d) of the FD&C Act. A finding of effectiveness must be supported by substantial evidence based on adequate and well-controlled clinical investigations.[26] A finding of safety must be supported by sufficient information (including adequate tests) to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling.[27]

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[24] For further information on REMS, see the guidance for industry *Format and Content of a REMS Document* (January 2023).

[25] See, for example, 21 CFR part 312, subpart E, Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses and the guidance for industry *Benefit-Risk Assessment for New Drug and Biological Products* (October 2023).

[26] See section 505(d) of the FD&C Act ("[T] the term 'substantial evidence' means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for the purposes of the preceding sentence."). See also the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998) and the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

[27] See section 505(d) of the FD&C Act.

As noted previously, use of a flexible antibacterial drug development program is consistent with the philosophy first formally articulated in regulations codified at 21 CFR part 312, subpart E.[28] This philosophy reflects the FDA's commitment to expediting the availability of drugs for serious diseases for patients as soon as it can be concluded that the drug's benefits exceed its risks, especially when these patients have unmet medical needs, while preserving appropriate standards for safety and effectiveness.

12. What are key aspects of the labeling of drugs developed under a flexible development program for the treatment of serious bacterial diseases in patients with an unmet medical need?

To obtain approval, a sponsor must, among other things, demonstrate that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling (section 505(d)(1) of the FD&C Act). Furthermore, it is important to emphasize the following points:

- Labeling for such drugs should include not only the known risks and benefits of the drug but also a description of the limitations of the available information that supported approval

- Postmarketing monitoring (or, in some cases, continued development of the drug), as well as postmarketing requirements or postmarketing commitments, can help to further define the drug's safety and efficacy profile (see the responses to Questions 9 and 11)

In addition, for drugs approved under the LPAD pathway, there are specific requirements regarding labeling and FDA review of marketing materials (see response to question 16).[29]

For all drugs, but particularly for drugs approved with a smaller safety database, important findings regarding safety may first become apparent in the postmarketing period.

13. What is the role of a rapid diagnostic in more flexible antibacterial drug development programs?

The use of rapid bacterial detection methods, such as urinary antigen tests, serology, and polymerase chain reaction, may help identify the baseline bacterial pathogen or pathogens. Development of these methods is particularly important for drugs that have a narrow spectrum of activity (e.g., drugs active against a single species or a few species within a genus), as delayed identification of the causative pathogen may result in a drug versus pathogen mismatch that could lead to unacceptable delays in appropriate treatment, delays in identification of eligible patients in the context of a clinical trial, or use of unnecessarily broad antibacterial therapy.

[28] See 21 CFR 312.80.

[29] See section 505(h)(3)(A) of the FD&C Act. See also the guidance for industry *Limited Population Pathway for Antibacterial and Antifungal Drugs*.

The clinical trial for a candidate antibacterial drug may provide an opportunity to contribute to the development and evaluation of a new diagnostic test. Sponsors are encouraged to discuss these approaches with the Agency.

14. Can an antibacterial drug approved for patients with an unmet medical need using a flexible development program be subsequently developed for other indications?

Yes, a sponsor can use a flexible development approach to obtain approval of an indication that addresses an unmet medical need, and subsequently develop the drug for other indications. Depending on the indication, a flexible or a traditional development approach may be used.

15. Does the approval of one drug for the treatment of a serious bacterial disease in patients with an unmet medical need preclude approval of another drug for the same indication using a flexible development program?

No. The approval of an antibacterial drug for the treatment of serious bacterial diseases in patients with an unmet medical need does not necessarily preclude the development of a subsequent drug for the same or similar indication using a flexible development program. Provided below are some examples for when an antibacterial drug may be considered to address an unmet medical need when there is an already approved treatment for the same indication:

- The first drug approved has serious adverse reactions limiting its use.
- The adverse reactions of the approved drug could affect its utility in certain subpopulations (e.g., a drug with the potential to cause nephrotoxicity would be a less than ideal choice in a patient with renal impairment). Another drug with a different adverse reaction profile (e.g., the drug is not associated with nephrotoxicity) could provide a treatment option for these patients.
- A subsequent drug may have a novel mechanism of action unaffected by existing mechanisms of resistance.
- The approval of more than one drug could address an anticipated public health need such as a drug shortage.

16. Are there special considerations for the INDICATIONS AND USAGE section of drug labeling?

For new antibacterial drugs that treat serious bacterial diseases in patients with an unmet medical need, the INDICATIONS AND USAGE section of labeling should include a statement that the drug is for use in patients who have limited or no alternative treatment options and summarize the limitations of available data that supported the approval (e.g., limited efficacy and/or safety data).[30] For additional recommendations for this section of labeling, see the draft guidance for industry *Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2018).[31] For drugs studied in trials in which serious infections at different body sites were studied (see Question 5), the scope of the indication(s) may depend on numbers of subjects enrolled with different infections, results in disease-specific subgroups, and consistency of effects across these subgroups.

For new antibacterial drugs to treat serious bacterial diseases in patients with an unmet medical need, FDA recommends use of the following (or similar) language in the INDICATIONS AND USAGE section of the labeling:

> DRUG-X is indicated, in *[age groups (e.g., adult)]* patients who have limited or no alternative options for the treatment of *[serious bacterial diseases such as hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, complicated intra-abdominal infections, complicated urinary tract infections (include as appropriate)]* caused by the following susceptible microorganism(s): *[list the genus and species of the bacterial pathogen(s)]*. Approval of this indication is based on *[summarize the limitations of available data that supported the approval]*.

For drugs approved under LPAD, the statement "Limited Population" must be included in a prominent manner in all labeling and advertising.[32] FDA recommends that this statement be included in the INDICATIONS AND USAGE section of labeling.[33]

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[30] Sponsors are obligated to comply with the content and format requirements of labeling for new antibacterial drugs under 21 CFR 201.24, 201.56(d), and 201.57. See the guidance for industry *Labeling for Human Prescription Drug and Biological Products—Implementing the PLR Content and Format Requirements* (February 2013). For additional Prescribing Information guidance documents, see the FDA's Prescribing Information Resources web page, available at https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources.

[31] When final, this guidance will represent FDA's current thinking on this topic.

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

[33] See the guidance for industry *Limited Population Pathway for Antibacterial and Antifungal Drugs*.