Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers (Revision 1)

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact Peter Kim (CDER) 301-796-0741.

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

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Guidance for Industry[1]

I. INTRODUCTION

This guidance is intended to assist sponsors in the clinical development of new antibacterial drugs.[2] Specifically, the guidance explains the FDA's current thinking about possible development programs and clinical trial designs for antibacterial drugs to treat serious bacterial diseases in patients with an unmet medical need, including patients with a serious bacterial disease for which effective antibacterial drugs are limited or lacking.[3] 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 in patients with an unmet medical need.[4] For products that have the potential to address an unmet medical need, a more flexible development program may be acceptable to facilitate development.

Section 3042 of the 21st Century Cures Act (Public Law 114-255) established a limited population pathway for certain antibacterial and antifungal drugs (LPAD) that are intended to treat a serious or life-threatening infection in a limited population of patients with unmet medical

[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] For example, effective antibacterial drugs can be limited because resistance to several antibacterial drugs has developed. Patients who have allergies or intolerance to several antibacterial drugs also may be considered as having an unmet medical need. See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014), section III. C., Unmet Medical Need. 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.

[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*.

needs.[5] Antibacterial and antifungal drugs developed to address unmet medical need may also be considered for approval under the LPAD pathway.[6] Sponsors are encouraged to discuss proposed approaches with the Agency.

This draft guidance revises the guidance for industry *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases* (August 2017). After it has been finalized, this draft guidance will replace the August 2017 guidance. Significant changes in this draft guidance from the 2017 version include the possibility to conduct noninferiority trials that include subjects with infections caused by certain drug-resistant pathogens since effective active controls are now available. More detail is also provided for the currently used noninferiority trial designs that may be used with a wider noninferiority margin, including cases for which the trial population is enriched for subjects with infections caused by certain drug-resistant organisms.

This draft 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.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, 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, and complicated urinary tract infections, who may not respond to currently available antibacterial drugs.[7]

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, which may obscure the effect of the antibacterial drug under study because empiric antibacterial therapy administered to some subjects before enrollment in the trial may be effective; (2) the severity of the acute illness in subjects (e.g., delirium in the setting of acute infection) may make obtaining informed consent and performing other trial enrollment procedures difficult; (3) the

[5] See section 506(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

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

[7] See the Bibliography at the end of this guidance.

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 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, sponsors should be aware of the recognized need for flexibility in 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), below.

> *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.*[8]

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.[9] Such drugs are likely to 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.

[8] See 21 CFR 312.80.

[9] 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*.

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 is a candidate for a more 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[10]

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?

Sponsors should evaluate the antibacterial activity of the new drug, mechanism of action, mechanism or mechanisms of resistance, 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.

To the extent that a flexible clinical development program involves smaller, shorter, 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. In certain circumstances, an abbreviated nonclinical program may be applicable (see Question 6 below). 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.[11] Other guidances for industry discuss the important elements of the nonclinical safety evaluation.[12] Sponsors are encouraged to discuss their nonclinical safety program with the Agency early in the development process.

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[10] 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 guidance for industry and Food and Drug Administration staff *In Vitro Companion Diagnostic Devices* (August 2014) and the guidance for industry and Food and Drug Administration staff *Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices* (February 2019).

[11] See 21 U.S.C. 355(d).

[12] 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 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* (July 1997), 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*

Flexible drug development programs that address an unmet medical need for serious bacterial infections may include clinical trials with smaller sample sizes and greater uncertainty. 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[13]
- Activity in appropriate animal models of infection[14]
- 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 animal models of infection, such as the PK/PD index that is associated with activity in a relevant animal model and/or in vitro model or 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
- Dose and frequency of administration that was evaluated in 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

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).

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

[14] 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.

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 treatment options, efficacy of an investigational drug can be established in a noninferiority trial.[15] The active comparator used in the trial should provide effective 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 demonstrating the activity of the investigational drug against resistant phenotypes.

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 of the comparator.[16] The primary analysis of noninferiority should exclude subjects with baseline pathogens resistant to the control drug.[17]

A trial could be enriched to enroll subjects with the pathogen or pathogens of interest. As new treatment options have become available, it is now possible to enroll subjects with infection caused by certain antibacterial drug-resistant phenotypes of interest that are 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 with confirmatory evidence to meet substantial evidence of effectiveness. Sponsors should discuss with the 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 (e.g., ventilator-associated bacterial pneumonia and complicated intra-abdominal infection) and inferential statistical evaluations for a finding of superiority.

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

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

[17] 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. See the response in Question 4.c., Nested noninferiority/superiority clinical trials.

Typically, superiority trials compare an investigational drug with an inactive placebo using a standard statistical significance level to control the risk of falsely declaring efficacy. However, in some circumstances, superiority against an active control that is considered best available therapy is more acceptable. Best available therapy may be expected to have some treatment benefit, although there may not be reliable and reproducible evidence to quantify this effect. In this situation, a superiority finding using a prospectively planned and agreed upon significance level corresponding to a less stringent type I error rate could be acceptable as evidence of efficacy.

A superiority trial design can also be used to test for drug activity against a single species (or a few species) of bacteria. A sufficient number of subjects for enrollment in a trial of a particular type of infection (e.g., ventilator-associated bacterial pneumonia) may not be available. Subjects with infections at more than one body site caused by the bacterial species of interest can be enrolled in the trial, with inferential statistical testing for superiority.[18]

c. Nested noninferiority/superiority clinical trials

Subjects can be included in a nested, active-controlled noninferiority/superiority trial design. In this trial design, the first step should be to demonstrate noninferiority of the investigational drug to the control treatment in the population of subjects who have a baseline bacterial isolate susceptible to the control drug. If noninferiority is demonstrated, the second step should be to evaluate superiority in subjects subsequently confirmed to be infected with a baseline bacterial isolate resistant to the control drug.[19] This hierarchical nested design does not require any multiplicity adjustments to control the overall type I error rate.[20] Given the sequential nature of the preplanned testing, there would be no statistical penalty for the evaluation of superiority if superiority testing is conducted only after noninferiority is established.

One could consider enriching the trial for pathogens of the resistance phenotype of interest as long as the comparator drug is likely to be effective as empiric therapy pending culture and susceptibility results. Subjects may be randomized to the investigational drug or the control drug before the availability of the results of antibacterial drug susceptibility testing of the baseline pathogens. The trial should include provisions for adjusting the control regimen to provide appropriate therapy based on the susceptibility test results. It is essential that adequate procedures be in place to protect subjects enrolled in this trial from avoidable exposure to less effective therapy.

[18] See the response to Question 17 for additional discussion on labeling considerations.

[19] See, for example, the nested noninferiority/superiority design in Infectious Diseases Society of America, 2012, White Paper: Recommendations on the Conduct of Superiority and Organism-Specific Clinical Trials of Antibacterial Agents for the Treatment of Infections Caused by Drug-Resistant Bacterial Pathogens, Clin Infect Dis, 55(8):1031–1046.

[20] See Huque MF, T Valappil, and G Soon, 2014, Hierarchical Nested Design for Demonstrating Treatment Efficacy of New Antibacterial Drugs in Patient Populations with Emerging Bacterial Resistance, Stat Med, 33(25):4321–4336.

5. Can subjects who have infections at different body sites be enrolled in the same clinical trial? If so, what are examples of primary efficacy endpoints and analysis considerations?

Yes. Superiority trials may be appropriate when enrollment of subjects with infections across body sites is preferred for study feasibility; for example, an antibacterial drug with activity against a single species (or a few species) of bacteria. Assuming noninferiority margins can be justified, a noninferiority trial design may be acceptable when closely related infections associated with similar disease severity and causative pathogens are combined, such as ventilator-associated bacterial pneumonia and bloodstream infections.

There may be several options to consider for a primary efficacy endpoint across multiple body sites. One option is to use different clinical efficacy endpoints based on each body site infection. Each subject would be counted as a *success* or *failure*, depending on the outcome specific to each body site infection, and results would be examined by each body site (recognizing the limited numbers available for each site). Another option for a primary efficacy endpoint is all-cause mortality if the types of infections in the trial are often fatal when untreated.

A more flexible development program that includes a trial enrolling subjects with infections at different body sites may not be able to identify antibacterial drugs that are less effective in some body sites compared with others. There have been several recent instances where unexpected results from clinical trials revealed reduced performance of an antibacterial drug for the treatment of severe infections at some body sites.[21] Trials should enroll subjects who have greater severity of illness to address concerns regarding the potential for reduced performance in some body sites. Sponsors should discuss with the Agency stratified enrollment or other approaches to ensure that a sufficient number of subjects with infections at certain body sites, such as the lung, are enrolled.

For example, such a trial of an investigational drug with activity against gram-negative bacteria could enroll subjects receiving care in an intensive care unit with one of the following different infections: (1) ventilator-associated bacterial pneumonia, (2) hospital-acquired bacterial pneumonia requiring mechanical ventilation or nonventilated hospital-acquired bacterial pneumonia with hypotension and/or bacteremia, (3) complicated intra-abdominal infection plus hypotension and/or bacteremia, and (4) complicated urinary tract infection plus hypotension and/or bacteremia. In this example, we recommend that subjects who have ventilator-associated bacterial pneumonia or hospital-acquired bacterial pneumonia requiring mechanical ventilation should comprise approximately 50 percent or more of the total subject population to adequately represent patients with more severe infections. Sponsors are encouraged to discuss plans for multisite studies with the FDA before they begin the trial.

Frequentist or Bayesian modeling approaches for assessing subgroup-specific treatment effects may be useful in trials designed to enroll subjects with body site infections that have different severity and associated comorbid conditions. Modeling approaches provide a measure of internal consistency of treatment effect among the subgroups of each body site.

[21] See Cox E, S Nambiar, L Baden, 2019, Needed: Antimicrobial Development, N Engl J Med. 380(8):783–785.

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

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.[22]

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 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.[23]

Collaboration between sponsors may assist in the development of antibacterial drugs with spectra of activity that do not overlap. For instance, if investigational Drug A and investigational Drug B are active against different species of bacteria and use of Drug A and Drug B together could be considered as complete empiric coverage for possible bacterial pathogens causing the infection, then a trial comparing Drug A plus Drug B to the best-available active control therapy could be used to evaluate each drug in the prespecified primary analysis populations based on the baseline bacterial species. Sponsors pursuing this approach should discuss with the FDA the safety data that would be needed to assess the individual antibacterial drugs.

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.

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[22] 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).

[23] Some trials may feature an adaptive design that includes several investigational drugs, each as a different treatment arm that is compared with a common control arm representing standard-of-care treatment. An example of an innovative trial design is the **I**nvestigation of **S**erial Studies to **P**redict **Y**our **T**herapeutic **R**esponse With **I**maging **A**nd Mo**L**ecular Analysis **2** (**I-SPY 2 TRIAL**). Information about the trial can be found at http://www.ispytrials.org/home.

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 administration for evaluation in clinical trials.[24] 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.[25]

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[24] 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).

[25] Nonclinical data and early safety data can inform the size of the premarketing safety database; see, for example, ICH guidances for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005) and *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs — Questions and Answers (R1)* (October 2012).

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 Federal Food, Drug, and Cosmetic Act (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 drug products.[26] Section 505-1 authorizes the FDA to require a risk evaluation and mitigation strategy (REMS) if the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh the risks of the drug.[27]

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.[28]

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.[29] A finding of safety must be supported by

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[26] 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. 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.

[27] For further information on REMS, see the revised draft guidance for industry *Format and Content of a REMS Document* (October 2017). When final, this guidance will represent the FDA's current thinking on this topic.

[28] See 21 CFR part 312, subpart E, Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses.

[29] 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

sufficient information (including adequate tests) to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling.[30]

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.[31] 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. Why is it important for the FDA and for sponsors to emphasize to the health care community the risks and benefits of drugs developed under a more 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). Therefore, drug labeling should identify the approved indication, including the targeted patient population. Furthermore, it is important to emphasize the following points:

- Product 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

- It is important for the health care community to be informed on how to use the drug appropriately (i.e., make clear the approved patient population for which the FDA has determined the benefits of the drug outweigh the risks)

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

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.

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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).

[30] See section 505(d)(1) of the FD&C Act.

[31] See 21 CFR 312.80.

13. Is the animal rule an appropriate consideration for a more flexible development program?

When human clinical effectiveness trials can be conducted, drugs are not eligible for approval under the so-called *animal rule*, a term that refers to the regulatory pathway set forth in 21 CFR part 314 subpart I (or, for biologics, 21 CFR part 601 subpart H) for approving drugs when human efficacy studies are not ethical or feasible.

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

The use of bacterial detection methods, such as urinary antigen tests, serology, and polymerase chain reaction, may help identify the baseline bacterial pathogen or pathogens. These methods could be particularly helpful for drugs that have a narrow spectrum of activity (e.g., drugs active against a single species or a few species within a genus).

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 and the appropriate review division in the Center for Devices and Radiological Health.

15. 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.

16. 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 effects limiting its use.

- The adverse effects 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 impaired renal function). A subsequent drug with a different adverse effect profile could provide a treatment option for these patients.

- The approval of more than one therapy addresses an emerging or anticipated public health need, such as a drug shortage or the development of antibacterial resistance. For instance, a drug may have a novel mechanism of action and not be affected by existing mechanisms of resistance.

17. Are there special considerations for the product labeling?

The labeled indication for a drug approved under a flexible development program should reflect the patient population for which the drug is approved (e.g., the patient population with a serious infection caused by a bacterial pathogen that the drug is intended to treat for which the patient has no treatment options or limited alternative treatment options available). The INDICATIONS AND USAGE section should also summarize the limitations of available data that supported the approval (e.g., limited efficacy and/or safety data).[32] If the development program is based on trials that enroll subjects with infections at different body sites, as discussed in Questions 4(b) and 5, then the indication or indications may depend on numbers of subjects enrolled with different diseases, results in disease-specific subgroups, and consistency of effects across these subgroups.

The following example represents wording for an indication based on use of a flexible development program for patients who have a serious infection in the setting of limited therapeutic options or no alternative treatment options:

> DRUG-X is indicated, in *[age groups (e.g., adult)]* patients *[who have limited or no alternative treatment options (include as appropriate)]* 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]*.

The FDA has issued a final guidance regarding LPAD, including specific labeling-related information.[33,34]

[32] Sponsors are obligated to comply with the content and format requirements of labeling for 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).

[33] See section 506(h)(3)(A) of the FD&C Act (as amended by the 21st Century Cures Act).

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

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