



# **FDA Webinar**

## **Guidance for Industry**

# **Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases**

**September 27, 2013**

# Conflict of Interest

Joseph G. Toerner, M.D., M.P.H.  
Associate Director for Medical Affairs  
Office of Antimicrobial Products  
CDER, FDA

- No conflicts



---

# **Guidance for Industry Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases**

*DRAFT GUIDANCE*

## **Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases**

- Draft guidance for comment
- Issued 1 July 2013; FR 2 July 2013
- Comments due 30 September 2013
- FDA considers comments as work begins to finalize the draft guidance

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## I. INTRODUCTION

This guidance is intended to assist sponsors in the clinical development of new antibacterial drug therapies.<sup>2</sup> Specifically, the guidance explains the FDA's current thinking about possible streamlined development programs and clinical trial designs for: (1) drugs to treat serious bacterial diseases in patients with unmet medical need; and (2) drugs that are *pathogen-focused* antibacterial drugs (e.g., drugs that have a narrow spectrum of activity or are only active against a single genus and species of bacteria) and are used for the treatment of serious bacterial diseases in patients who have an unmet medical need.<sup>3</sup> This draft guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective Products, pharmaceutical sponsors, the academic community, and the public on issues related to the clinical trial design for antibacterial drug products.<sup>4</sup> It is not intended to establish a new approval pathway or standard for such drug products.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## II. BACKGROUND

Over the last few decades, efforts to develop new antibacterial drugs have declined substantially. Over this same time period antibacterial drug resistance has become more common even in settings in which attempts were made to slow the rate at which bacterial pathogens become resistant, such as the prudent use of antibacterial drugs and adherence to infection control procedures. As a result, an increasing number of patients are suffering from bacterial diseases that do not respond to currently available antibacterial drugs, with serious consequences, including increased mortality.<sup>6</sup>

Generally, patients hospitalized with acute serious bacterial diseases are likely to include patient populations with unmet medical need. These acute bacterial diseases in hospitalized patients include hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), complicated urinary tract infection (cUTI), complicated intra-abdominal infection (cIAI), community-acquired bacterial pneumonia (CABP), acute bacterial skin and skin structure infection (ABSSSI), and other serious bacterial diseases. Appropriate antibacterial drug therapy may not be available to these patients, and therefore they may have unmet medical need, because the bacterial pathogen causing the infection is resistant to multiple antibacterial drugs or is an emerging pathogen for which no antibacterial therapy has yet been developed. In some cases, a patient's intolerance or allergy to available antibacterial drugs may limit available therapies.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## II. BACKGROUND

Clinical trials for antibacterial drugs can be challenging for a number of reasons, including: (1) for a serious bacterial disease, there is a need to urgently initiate empiric antibacterial drug therapy, which may obscure the effect of the antibacterial drug under study because patients receive effective antibacterial therapy before enrolling in the trial; (2) patients with serious acute bacterial diseases can be acutely ill (e.g., delirium in the setting of acute infection) and obtaining informed consent and performing other trial enrollment procedures in a timely fashion may be difficult; (3) there may be diagnostic uncertainty with respect to the etiology of the patients' underlying disease, including identifying a bacterial etiology; and (4) there may be a need for concomitant antibacterial drug therapy with a spectrum of activity that may overlap with the antibacterial drug being studied.

A decreased rate of antibacterial drug development poses a significant public health concern. As bacteria continue to develop resistance because of selection pressures from empiric and/or inappropriate use of currently available antibacterial therapies, increased numbers of patients will have unmet medical need related to effective antibacterial drug therapy. Therefore, it is important for the public health that new antibacterial drugs be developed while also considering how best to ensure appropriate use.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## II. BACKGROUND

To foster development of new antibacterial therapies for the treatment of serious bacterial diseases, we are exploring approaches that may help streamline development programs for antibacterial drugs, especially for drugs that could address an unmet medical need. As recognized in FDA regulations for the evaluation of 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 drugs that treat life-threatening and severely-debilitating illnesses, than they would accept from drugs 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.”<sup>7</sup>*

<sup>7</sup> See 21 CFR 312.80, subpart E, Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## III. QUESTIONS AND ANSWERS

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

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 1. What types of antibacterial drugs may be appropriate for a streamlined development program?

Possible candidates for a streamlined development program are antibacterial drugs intended to treat serious bacterial infections in patients who have unmet medical need.<sup>8</sup> Because these drugs will be developed to treat infections in patients who have few or no treatment options, they are likely to be drugs that: (1) act via new mechanisms of action; (2) have an added inhibitor that neutralizes a mechanism of resistance; or (3) have an alteration in the structure of the molecule that makes the drug no longer susceptible to the mechanism of resistance to existing drugs. Due to the paucity of available therapies for many patients with bacterial infections, antibacterial drugs that are intended to treat patients with intolerance or allergy to currently available drugs are also likely to be considered to address an unmet medical need. In contrast, a drug that has slightly greater potency (e.g., more active by a 2 to 3 dilutions in vitro testing) generally would not be considered a drug that addresses an unmet need and should undergo a traditional development program.

<sup>8</sup> For a more general discussion of the concepts of *unmet medical need* and *serious conditions*, see the draft guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*. When final, this guidance will represent the FDA's current thinking on this topic.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 1. What types of antibacterial drugs may be appropriate for a streamlined development program?

A drug that treats a single genus and species of bacteria causing a serious bacterial disease also is a possible candidate for a streamlined development program, particularly when intended to treat patients with unmet medical need. For an antibacterial drug active against only a single genus and species, the clinical trial design should be discussed with the FDA (e.g., pathogen-focused antibacterial drug development). Sponsors should consider the following factors:

- The frequency with which the genus and species of interest causes serious infections
- The ability to identify patients with the bacterial pathogen of interest; standard culture and in vitro susceptibility testing often take 2 days or more to identify the bacterial pathogen of interest
- The potential of rapid diagnostic tests to identify patients with the bacterial pathogen of interest for prompt enrollment into a clinical trial of a pathogen-focused antibacterial drug
- The availability of rapid diagnostics to detect the genus and species of interest, which could be essential to the study of the drug for the demonstration of clinical benefit

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**

Different approaches can be used to evaluate an antibacterial drug for the treatment of a serious bacterial disease in patients with unmet medical need. The four approaches outlined below are provided as examples of streamlined development programs that sponsors may consider using. These four approaches are not intended to be mutually exclusive; in some cases combining elements from across these approaches may be appropriate. Sponsors are encouraged to discuss their specific proposed development programs with the FDA before commencing clinical trials.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**

In each of the approaches discussed below the development program provides important nonclinical information on:

- The in vitro activity of the investigational drug
- The mechanism of action of the drug and whether mechanisms of resistance to other drugs affect the investigational drug's activity
- The evaluation of pharmacokinetic/pharmacodynamic (PK/PD) relationships from animal models of infection
- Activity of the investigational drug in animal models of infection; these studies may provide important information evaluating the activity of an investigational antibacterial drug at particular body sites (e.g., pneumonia)

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**
  - a. **Prospective active-controlled clinical trials in patients with serious bacterial diseases and unmet medical need**

An investigational drug can be compared to the best-available active-control therapy in a randomized controlled trial, with the intent of showing superiority of the investigational drug, because the best-available therapy may be suboptimal. Such a trial can be conducted in a patient population enriched for an unmet need; for example at trial sites that have a high frequency of infections caused by bacterial pathogens associated with unmet medical need. The trial could study a single infection site (e.g., cIAI), but it also could enroll patients with bacterial disease at any one of several different body sites; the prespecified endpoints for these trials should be discussed with the FDA.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**
  - a. **Prospective active-controlled clinical trials in patients with serious bacterial diseases and unmet medical need**

A finding of superiority based on a randomized comparison and a well-defined and reliable clinical endpoint is readily interpretable evidence of effectiveness. Sample size estimates for a trial intended to show substantial superiority generally are smaller than those for a noninferiority trial, depending on the noninferiority margin. For example, approximately 97 patients per arm would be an adequate sample size estimate (90 percent power and two-sided type I error of 0.05) for a study in which the active-control group is expected to have a 65 percent success rate and the investigational drug group is expected to have an 85 percent success rate.<sup>9</sup> Such a result could occur only if the population studied had a high rate of patients with serious bacterial diseases and unmet medical need (e.g., a high rate of patients with bacterial pathogens resistant to most antibacterial drugs). The sample size also could be reduced by allowing for a different significance level; for example a one-sided type I error of 0.05 rather than a two-sided significance level.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**
  - a. **Prospective active-controlled clinical trials in patients with serious bacterial diseases and unmet medical need**

For trials in patients with unmet medical need, it often may be the case that few patients are enrolled at each clinical center. In this case, consideration could be given to randomizing centers rather than individual patients, with appropriate adjustments to the statistical analysis plan to accommodate cluster randomization. This strategy, with appropriate informed consent procedures, could facilitate trial conduct by allowing for streamlined enrollment procedures and possibly minimizing the need to administer antibacterial drug therapy to patients before randomization. Patients enrolled at sites randomized to the standard-of-care arm would be treated no differently than is usual practice at that site, while patients enrolled at sites randomized to the investigational drug arm would be treated with the investigational drug.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**
  - a. **Prospective active-controlled clinical trials in patients with serious bacterial diseases and unmet medical need**

Innovative design and analysis strategies (including randomization of clinical trial centers, adaptive design clinical trials, Bayesian design and analysis strategies, or other approaches) can be employed in prospective, active-controlled trials, with an opportunity to stop the trial early for efficacy or futility.<sup>10</sup> For example, the adaptive design might result in a shorter overall duration of the trial based on modification of sample size as a result of observed rates of patients enrolled who have unmet medical need. As another example, Frequentist (e.g., logistic regression models) or Bayesian modeling approaches for assessing subgroup-specific treatment effects may be useful in trials designed to enroll patients with infections at any one of several different body sites, where the infection site defines a subgroup of interest.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**
  - a. **Prospective active-controlled clinical trials in patients with serious bacterial diseases and unmet medical need**

Another approach is a nested, active-controlled, noninferiority/superiority trial design in which patients are randomized to investigational drug or control drug at the beginning of therapy before the availability of the results of antibacterial drug susceptibility testing. Patients subsequently confirmed to be infected with the relevant pathogen associated with an unmet medical need on the basis of the results of in vitro susceptibility testing would be examined as a distinct subgroup for superiority.<sup>11</sup> Patients confirmed to be infected with standard pathogens (i.e., not a pathogen associated with an unmet medical need) would be examined in a distinct noninferiority analysis that evaluates the ability of the drug to treat the infection under consideration with a noninferiority margin that reflects the recognition that the benefits of the drug need to be evaluated in light of the severity of the unmet medical need.<sup>12</sup> The noninferiority component of the study would demonstrate the antibacterial activity of the drug while the smaller subset of patients with the pathogen associated with an unmet medical need should demonstrate a greater effect in that population.

<sup>11</sup> 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.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**
  - b. **External control or historical control clinical trial in patients with serious bacterial diseases who have unmet medical need**

A clinical trial design that relies on a historical or external control may be acceptable to evaluate efficacy in a patient population with an unmet need, in particular a patient population in which standard-of-care therapy is suboptimal and the investigational drug shows activity in nonclinical and early clinical development such that withholding the investigational drug may be considered unethical. This trial design type generally is acceptable when the untreated morbidity is high and does not vary widely in the patient population enrolled in the trial, and the effect of the investigational drug is expected, based upon early clinical or nonclinical data, to be large compared to historical experience. The outcomes among patients with unmet medical need who received the investigational drug should be compared to the outcomes in an external control group, and should be expected to show a large treatment benefit for the investigational drug, because of concerns regarding potential bias from cross-study comparisons. The information needed to evaluate the historical control response rate is fairly similar to what is needed to support a noninferiority margin in an active-controlled trial, although the goal of the trial is different. In a noninferiority trial, one is seeking similarity to the best-available therapy (i.e., ruling out an unacceptable difference). In the case of the historical control trial, one is seeking an advantage over what is essentially no treatment.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**
  - b. **External control or historical control clinical trial in patients with serious bacterial diseases who have unmet medical need**

Sponsors considering a trial design that relies on a historical control based on a retrospective review should characterize the proportion of patients with the clinical outcome of interest when given no therapy or inadequate therapy. Current antibacterial drug development guidances contain information on retrospective reviews of outcomes when patients were given no therapy or inadequate therapy in specific disease conditions. These guidances may be helpful to sponsors interested in using historical controls and provide examples of approaches that have been used in developing noninferiority margins.<sup>13</sup>

For an externally controlled trial, the control patients should be as similar as possible to the population expected to receive the investigational drug in the trial, and they should have been treated in a similar setting and in a similar manner, except with respect to the investigational drug therapy.<sup>14</sup> Currency of the historical control group also should be considered, so that the comparison between the investigational drug and control group is based on the most recent relevant experience with the control drug as is available.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**
  - b. **External control or historical control clinical trial in patients with serious bacterial diseases who have unmet medical need**

For externally controlled trials or historical controlled trials in which the primary statistical comparison is between the investigational drug and the external or historical control, sponsors should consider the possibility of randomizing at least a small number of patients to the active control in the trial (e.g., through disproportionate randomization of 3:1, 4:1, among others), if feasible, based on an active control considered to be the best-available therapy. Both Frequentist and Bayesian statistical methods can then be used to incorporate historical or external control data with data from the patients randomized to the active control in assessing treatment group differences for the primary comparison. Data external to the trial can be down-weighted relative to the concurrent control data to reflect lesser comparability, as needed.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**
  - c. **Noninferiority clinical trials in patients with serious bacterial diseases with treatment options to provide evidence of efficacy supporting use for patients with unmet medical need**

An investigational drug intended to treat serious bacterial diseases in patients with unmet medical need can have efficacy established primarily on the basis of disease-specific noninferiority clinical trials enrolling patients with a particular serious bacterial disease for whom other treatment options are available.<sup>15</sup> These trials should prespecify a supportable noninferiority margin based on the historical evidence of active-control treatment effect, if available. If not, for severe bacterial diseases in which the magnitude of treatment effect is known to be substantially large, a noninferiority margin based on other sources of information or on clinical judgment could be considered. The choice of the margin should be discussed with the FDA in advance of trial initiation.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. **What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?**
  - c. **Noninferiority clinical trials in patients with serious bacterial diseases with treatment options to provide evidence of efficacy supporting use for patients with unmet medical need**

The performance of the active-control drug in the current trial should be evaluated for establishing a reliable and large treatment effect in the patient population of interest. Given that the investigational drug would be considered only for patients who do not have other treatment options and thus only where there is an unmet need, the characterization of efficacy in the noninferiority disease-specific trial could be based on different assumptions about type I and type II error or on the use of a larger noninferiority margin that still falls within the treatment effect of the active control. The level of certainty about efficacy could have greater flexibility than would be needed for a broader claim because of the recognition that the benefits of the drug need to be evaluated in light of the severity of bacterial diseases in patients with unmet medical need.<sup>16</sup> In addition to the noninferiority trial, PK/PD, safety, and outcome assessment data can be described from a trial that enrolls patients with serious bacterial diseases and unmet medical need who were treated with the investigational drug.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

2. What are possible approaches to a streamlined development program for an antibacterial drug for the treatment of patients with serious bacterial diseases and unmet medical need?

- d. Accelerated approval based on a surrogate endpoint

Accelerated approval may be appropriate when there is a surrogate or clinical endpoint reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Sponsors interested in pursuing a clinical development program using accelerated approval should discuss the choice of such an endpoint with the FDA. After approval based on a surrogate endpoint, postmarketing studies are required to verify and describe the clinical benefit (21 CFR 314.510, subpart H, or 21 CFR 601.41, subpart E).

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 3. Can the nonclinical development program associated with a streamlined clinical program also be smaller or streamlined?

In general, the answer is no. Information about chemistry, manufacturing, and controls and nonclinical toxicology studies are expected to be included in an investigational new drug application.<sup>17</sup> To the extent that a streamlined clinical development program involves smaller, shorter, or fewer clinical trials, it is likely that less quantitative data will be generated from clinical trials. Note that a sponsor developing a drug using a streamlined clinical development program must still provide adequate data to demonstrate that the drug is safe and effective to meet the statutory standard for approval.<sup>18</sup> In such programs involving antibacterial drugs, the other nonclinical studies may assume an even more important role in contributing to the assessment of the drug's antibacterial activity, the dose and dosing regimen to be evaluated in patients, mechanisms of drug metabolism, and adequate distribution of the antibacterial drug to relevant tissue sites. See other guidances for industry, which discuss in more detail these important elements of nonclinical development considerations.<sup>19</sup>

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 3. Can the nonclinical development program associated with a streamlined clinical program also be smaller or streamlined?

Data from nonclinical development should support the selection of a dose and frequency of administration to study in the clinical setting. In addition, the nonclinical data package should provide information on the following:

- The mechanism of action of the drug and whether mechanisms of resistance to other drugs affect the investigational drug's activity
- The in vitro activity of the investigational drug, including the minimum inhibitory concentration (MIC) from a representative sample of target bacterial pathogens
- Dose and frequency of administration that can be evaluated in in vitro models of infection using PK parameters obtained from human PK studies
- Evidence for the antibacterial drug's ability to achieve appropriate levels in relevant tissue sites from nonclinical studies (e.g., from animal models of infection)

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 3. Can the nonclinical development program associated with a streamlined clinical program also be smaller or streamlined?

Data from nonclinical development should support the selection of a dose and frequency of administration to study in the clinical setting. In addition, the nonclinical data package should provide information on the following:

- Activity of the investigational drug in animal models of infection
- The evaluation of the PK/PD index that is associated with efficacy in a relevant animal and/or in vitro model(s), based on the following:
  - Area under the plasma concentration time curve over the MIC
  - Maximum plasma concentration over the MIC
  - Time above MIC
- The target value of the PK/PD index that is associated with efficacy in the animal model

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 4. What is the importance of PK/PD (exposure-response) data in a streamlined development?

Information on the distribution of MIC for the target pathogen based on recent surveillance data, the results of PK/PD (exposure-response) assessments in animals, and results from human PK trials should be integrated to help identify the appropriate dose and frequency of administration for evaluation in clinical trials.<sup>20</sup> The PK information from humans should include information about the distribution of the drug to the action site (e.g., endothelial lining fluid obtained via bronchio-alveolar lavage for the lungs). Comparison of human and animal exposure data should include correction for any differences in plasma protein binding.

<sup>20</sup> See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* and the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration*.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 4. What is the importance of PK/PD (exposure-response) data in a streamlined development?

Collection of PK data in clinical trials (e.g., sparse sampling in all patients enrolled in clinical trials) may help in considering 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 unmet medical need often have important comorbidities, notably renal or hepatic impairment, and, therefore, an increased likelihood of alterations in pharmacokinetics. An important consideration in the conduct of trials is to characterize pharmacokinetics in such patients. For example, understanding the pharmacokinetics of the investigational drug in patients with renal or hepatic impairment early in development could facilitate enrollment in clinical trials of such patients (e.g., by providing guidance on dosing).

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 5. What are possible appropriate efficacy endpoints for a streamlined development program?

Possible endpoints include the endpoints described in the individual disease-specific guidances, clinical response endpoints, or a survival endpoint for the serious bacterial disease(s) being studied. Selection of appropriate endpoints depends upon the specific serious bacterial disease being studied. Sponsors should discuss with the FDA the efficacy outcome assessments appropriate to each specific infectious disease.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 6. What is the size of the premarketing safety database when considering streamlined development?

The premarketing safety database of an investigational drug should be appropriate to its potential benefit. A development program for a drug intended to treat a population of patients with unmet medical need generally would likely have a more limited safety database than would be expected for a drug with broader use to the extent it involves smaller, shorter, or fewer clinical trials. In general, a safety database for a drug that is the subject of a streamlined development program should include approximately 300 patients at the dose and duration of therapy proposed for marketing.<sup>21</sup> This safety database may include patients with the same proposed bacterial disease, but who do not have an unmet need (i.e., do not have an infection caused by a resistant form of the pathogen or who are not allergic or intolerant to currently available therapies).<sup>22</sup>

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 7. Will the FDA accept greater uncertainty about adverse effects?

With all drugs, adverse effects may become apparent only after a drug is marketed and used more widely. To the extent a clinical development program involves smaller, shorter, or fewer clinical trials, there likely will be greater uncertainty about the safety of the drug. Nonclinical and early clinical development data may be helpful in predicting such risks. Postmarketing monitoring (e.g., postmarketing requirements) or, in some circumstances, continued development of the drug by the applicant, will help to further define the drug's safety profile.

It is also possible that some drugs with risks that would be unacceptable for a broad population could be acceptable for patient populations that do not have other treatment options. As stated previously, balancing greater uncertainty or higher risk with an unmet need is an appropriate approach to benefit and risk assessment.<sup>23</sup>

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 8. 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 streamlined development program for the treatment of serious bacterial diseases in patients with unmet medical need?

To obtain approval, a drug sponsor must demonstrate that its drug is safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling. Therefore, a drug's labeling should include the limitations of the approved use, including any limitations on the approved patient population and any limitations on the available data for drugs developed under such programs. 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 by the applicant) can help to further define the drug's safety and efficacy profile

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

- 8. 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 streamlined development program for the treatment of serious bacterial diseases in patients with unmet medical need?**

For all drugs, but particularly for drugs supported by smaller, shorter, or fewer clinical trials, important findings regarding safety or new limitations of efficacy may first become apparent in the postmarketing period. Adequate steps to identify such important safety or efficacy findings early, and appropriately address the risks they pose, will be important for streamlined development programs.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## **9. Is the animal rule an appropriate consideration for a streamlined development program?**

No, because human clinical effectiveness trials can be conducted, drugs that are the subject of this guidance are not eligible for approval under the animal rule, as set forth in 21 CFR part 314, subpart I, Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 10. What is the role of a rapid diagnostic in streamlined antibacterial drug development programs?

The use of bacterial detection methods, other than culture, may help define the population identified to have a bacterial pathogen. Examples of nonculture detection of bacterial pathogens include urinary antigen tests, serology, and polymerase chain reaction.

The clinical trial for a candidate antibacterial drug may provide an opportunity to contribute to the development and evaluation of a new diagnostic test.<sup>24</sup> Sponsors are encouraged to discuss these approaches with the Division of Anti-Infective Products and the appropriate review division in the Center for Devices and Radiological Health.

The development and use of rapid detection methods should be helpful in identifying patients with the particular pathogen for drugs that have a narrow spectrum of activity (e.g., drugs only active against a single genus and species).

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## **11. Can an antibacterial drug be developed using a streamlined approach for patients with an unmet medical need and subsequently for other indications?**

Yes, a sponsor can use the streamlined development approach to obtain approval of an indication that addresses an unmet medical need, and subsequently develop the drug for other indications.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## **12. Does the approval of one drug for the treatment of a serious bacterial disease in patients with unmet medical need preclude approval of another drug for the same indication using a streamlined development program?**

No. The approval of an antibacterial drug for the treatment of serious bacterial diseases in patients with unmet medical need does not necessarily preclude the development of a subsequent drug for the same or similar indication using a streamlined development program. For example, a drug with a different mechanism of action, an alteration in its structure that makes the drug no longer susceptible to mechanisms of resistance, or use of the drug with an inhibitor that neutralizes a mechanism of resistance, may provide options for patients with certain infections either in the present or in the future as resistance develops, and would be considered to address an unmet medical need. In addition, under the following circumstances, an antibacterial drug may be considered to address an unmet medical need when there is an already approved treatment for the same indication:

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## **12. Does the approval of one drug for the treatment of a serious bacterial disease in patients with unmet medical need preclude approval of another drug for the same indication using a streamlined development program?**

an unmet medical need. In addition, under the following circumstances, 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 is found to have serious adverse effects in the postmarketing period that significantly affect its assessment of risk and benefit.
- The adverse effects of the first 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 antimicrobial resistance.

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## **13. Are there special considerations for the INDICATIONS AND USAGE section of product labeling?**

The labeled indication for drugs approved under a streamlined development program should reflect the patient population for which the drug is approved (i.e., the patient population with serious infections caused by a bacterial pathogen for which the unmet medical need exists). The INDICATIONS AND USAGE section should also summarize the limitations of available data that supported the approval (e.g., limited safety data).

# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

## 13. Are there special considerations for the INDICATIONS AND USAGE section of product labeling?

The example below represents wording for an indication whose approval was based on a streamlined development program for patients with serious infections with unmet medical need.

*Drug X is indicated, in [approved patient population], for the treatment of [HABP/VABP, cIAI, ABSSSI, CABP, cUTI (include as appropriate)] caused by the following susceptible microorganism(s): [list the genus and species of the bacterial pathogen(s)]. Drug X has been approved for use in patients with [HABP/VABP, cIAI, ABSSSI, CABP, cUTI (include as appropriate)] where limited or no alternative therapies are available. The safety and effectiveness of Drug X have not been established beyond this patient population. This indication is based on (summarize the limitations of available data that supported the approval).*



# Unmet Medical Need for the Treatment of Serious Bacterial Diseases

Thank you!

Please send comments to Docket No.  
FDA-2013-D-074 at [www.regulations.gov](http://www.regulations.gov).