

**Office of Antimicrobial Products**

**Briefing Document**

**Clinical Development Issues for Antibacterial Drugs for Patients with Unmet Medical Need  
for the Treatment of Serious Bacterial Diseases**

**Anti-Infective Drugs Advisory Committee**

**December 4, 2014**

## **DISCLAIMER STATEMENT**

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## 1. Introduction

The purpose of this background document is to provide summary information regarding the clinical development of antibacterial therapies for patients with an unmet medical need for the treatment of serious bacterial diseases. Some patients are experiencing infections caused by bacteria for which we have few or no available treatment options. It is essential that there be ongoing development of antibacterial drugs in order to address unmet medical needs.

The discovery and clinical use of antibacterial drugs during the 1930s and 1940s led to reductions in mortality rates for patients with serious bacterial diseases. The success of antibacterial drugs in treating pneumonia led to the more widespread use of antibacterial drugs for treatment of a variety of different types of infections, including, for example, respiratory tract infections of lesser severity that may be self-limited. Over time with more widespread use of antibacterial drugs, even with antibacterial drugs used appropriately, the selection pressures have resulted in bacteria that are resistant to antibacterial drugs. While new antibacterial drug development during the past century generally kept pace with the emergence of resistant bacterial pathogens, more recently the pace of new antibacterial drug development has slowed. Some patients now have bacterial infections with organisms susceptible to very few or no approved antibacterial drugs.

The clinical development of antibacterial drugs for the patient population with an unmet medical need is challenging. Affected patients can be rare and it may be difficult to identify such patients for enrollment in a phase 3 trial. If there is a documented outbreak, for example, of infections caused by resistant bacteria in a hospital's intensive care unit, infection control efforts to thwart the outbreak are often successful.<sup>1</sup> On the other hand, the recent experiences with methicillin-resistant *Staphylococcus aureus* (MRSA) infections emphasize the concern that resistant bacteria once limited to specific patient populations (e.g., hospitalized patients) can arise and spread commonly in a community setting.<sup>2</sup> A robust pipeline of new antibacterial drugs in development is important to be able to keep pace with a growing concern of the potential for more commonplace bacterial resistance.

This background document explores the regulatory history of antibacterial drug approvals that is necessary to understand the current framework for development of new antibacterial drugs. The document will also explain different strategies for a “streamlined” approach to clinical development, for which we seek the committee discussion and comments.

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<sup>1</sup> See, e.g., Snitkin ES, Zelazny AM, Thomas PJ, et al. Tracking a hospital outbreak of carbapenem-resistant *Klebsiella pneumoniae* with whole-genomic sequencing. *Sci Transl Med* 2012;4(128): 148ral16. doi:10.1126/scitranslmed.3004129.

<sup>2</sup> Okuma K, Iwakawa K, Turnidge JD, et al. Dissemination of new methicillin-resistant *Staphylococcus aureus* clones in the community. *J Clin Microbiol* 2002;40(11): 4289-4294.

## 2. Regulatory Background

The regulatory history for antibacterial drug approval covers a total of approximately 75 years, dating back to the 1930s. Earlier in the 20<sup>th</sup> century, the initial antibacterial drug approvals were not required to show efficacy. Later in the 20<sup>th</sup> century, antibacterial drug approvals were based on the equivalence or noninferiority trial design and, in some cases, a clear demonstration of efficacy was not evident based on the noninferiority trial design. Adequate and well-controlled clinical trials form the basis for modern day drug approvals. This regulatory background section provides an overview of past regulatory approaches and helps to provide a framework for the currently recommended drug development programs for new antibacterial drugs.

During the time period from 1938 until the 1962 Kefauver-Harris Amendments to the Food Drug and Cosmetic Act were enacted, antibacterial drugs were not required to show efficacy. Approvals were based upon assessments of safety along with adequate controls in manufacturing and batch certification. As part of the Drug Efficacy Study Implementation Review (DESI) following the 1962 Amendments, the efficacy of each antibacterial drug approved between 1938 and 1962 was assessed. The Indications and Usage section of labeling for drugs that were evaluated as part of the DESI review focused on the bacteria for which the antibacterial drug had demonstrated clinical activity rather than at a specific body site of infection (e.g., see the product labeling for penicillin G potassium injection<sup>3</sup>). The Warnings and Adverse Events sections for these products were based on clinical and laboratory safety observations from the available clinical data.

The 1962 Kefauver-Harris Amendments to the Food Drug and Cosmetic Act required the FDA to assess efficacy as well as safety of all approved drugs, and therefore pre-approval evaluations of efficacy as well as safety were required before a drug could be marketed. The labeled indications for an antibacterial drug would depend on what types of infections were observed among subjects enrolling in clinical studies. To illustrate the types of clinical studies that were used to support approvals after 1962, a few examples of the types of studies that were used to support approval of two different antibacterial drugs in the late 1960s are described below. These examples are meant to illustrate the general approach to antibacterial drug development during that period.

In the first example, the following studies were used to support the approval of an antibacterial drug. Studies of the antibacterial drug in healthy volunteers are described in the first bullet point and studies in patients with clinical infections are described in the second bullet point.

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<sup>3</sup> Product labeling is available at the DailyMed Web site which can be accessed at <http://dailymed.nlm.nih.gov/dailymed/about.cfm>.

- Studies were performed in healthy volunteers who were randomized to one of four study arms: the test drug at a “high” dose, test drug at a “low” dose, comparator antibacterial drug, or placebo. Serum samples were obtained from subjects to assess serum activity of each of the high- and low-dose test drug. Serum activity was assessed by testing the titer of antimicrobial activity of patient serum in an *in vitro* assay. Systematic clinical and laboratory safety evaluations were conducted during the study. This study enrolled just over 200 subjects. Two other safety studies in healthy volunteers that enrolled approximately 120 subjects were also performed. These three studies in healthy volunteers could assess antibacterial activity in blood via *in vitro* studies but gave no information about the effectiveness of the drug in any clinical illness.
- The efficacy and safety studies that were performed with this drug are best described as collections of case reports from patients with any of a variety of different types of bacterial infections. The case reports were grouped into subsets such as “lower respiratory tract infections”, as well as other types of infections. There was no control group in the study. Many of the case reports appear to have been considered inadequate to allow for evaluation of the case and hence were excluded by the FDA reviewer. For example, in this application approximately 900 case reports were submitted, and almost half of the case reports were found to contain inadequate information as determined by the FDA clinical reviewers. The total number of cases in the subset of “lower respiratory tract infection” that was evaluated in this study was approximately 35. A formal definition of clinical response was not apparent; the clinical responses were assessed to be “cured” or “not cured”. Safety data were not collected in a systematic fashion, and the safety data obtained and reported appear to have been largely determined by the practice of the investigator.

The studies described in the two bullets above appear to be the main clinical studies that supported approval of the antibacterial drug that was being evaluated, including the indication for treatment of lower respiratory tract infections.

In the second example, the application for another antibacterial drug included the following types of studies.

- A study was conducted in healthy volunteers to collect safety information in which subjects were randomized to one of three groups; test drug, a comparator antibacterial drug, or placebo. Approximately 80 healthy volunteers were enrolled in the study. Adverse event data were collected from subjects in the study.
- An uncontrolled study was conducted that is probably best described as a collection of case reports from patients with any of a variety of infectious diseases that were treated with the test drug. This study appears to have enrolled approximately 600 patients, and

safety data collection appears to be based upon investigator practice. Clinical responses were judged by the investigator to be “favorable” or “not favorable”. There is information on the types of infections in the “upper respiratory tract infection” subset, which included subjects with pharyngitis, tonsillitis, otitis media, sinusitis, tracheobronchitis, laryngotracheitis, and “mixed” infections. The “lower respiratory tract infection” subset included subjects who had pneumonia, bronchopneumonia, bronchitis, lung abscess, bronchiolitis, and bronchiectasis. The proportion of subjects within each of these different subgroups was widely variable.

These examples provide a sample of the types of information that were included in antibacterial drug applications from the late 1960s and the types of information that supported approval. The Indications and Usage section of antibacterial drugs approved during this time period usually describe the particular isolates of “susceptible bacteria” and included general categories of infections, such as “treatment of respiratory tract infections.” The Adverse Events section of product labeling described the safety observations that were noted among the available data. The studies used to evaluate efficacy generally lacked a control group and were analyzed by sub-setting the population of the cases gathered into groups of infections (e.g., “upper respiratory tract infections”). The studies lacked a pre-specified definition of a favorable clinical response and thus patients were categorized in a subjective manner as having favorable clinical responses to study drug.

An FDA document on anti-infective drug development from 1977 described clinical evaluations that were consistent with the types of evaluations done for antibacterial drug approvals during this time period.<sup>4</sup> The document stated the purpose of phase 3 studies was to “evaluate the usefulness of the drug in a wide variety of conditions, so as to obtain a broad picture of safety and efficacy.” Randomized, controlled clinical studies were not specifically discussed as part of phase 3 study designs. However, the document stated that “the therapeutic response to a new drug may be compared with the therapeutic response obtained by an earlier regimen, preferably one with which the investigator has experience in the same institution.”

As the science of clinical trial designs and our understanding of the pathophysiology of bacterial infections advanced, in the late 1980s and early 1990s there was a shift in the types of study designs that FDA was recommending to provide evidence to evaluate efficacy of an antibacterial drug. In addition, the randomized controlled clinical trial emerged as an optimal scientific method for evaluation of new drugs. In fact, new regulations were promulgated in 1985 that describe the characteristics of adequate and well-controlled studies.<sup>5</sup> During the 1990s (and

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<sup>4</sup> Guidelines for the Clinical Evaluation of Anti-Infective Drugs (Systemic Adults and Children). September 1977. Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM133315.pdf>

<sup>5</sup> §21 CFR 314.126: “Adequate and well-controlled studies”.

subsequently), FDA recommended clinical trials that were designed to enroll patients with infections involving a particular body site, rather than patients with any of a variety of different types of infections. There are differences among each of the body site infectious diseases in the following characteristics: 1) the efficacy endpoint; 2) the dose of an antibacterial drug; 3) the duration of antibacterial therapy; and, 4) the effectiveness of an antibacterial drug. In other words, the same antibacterial drug may require different doses and duration of therapy for different body sites and the drug may not be effective for certain body sites of infection. These recommendations are described in documents that provide advice on designing clinical trials to evaluate antibacterial drugs for each of a variety of different infectious diseases. These documents include the Infectious Diseases Society of America (IDSA) and the FDA Guidelines for the Evaluation of Anti-Infective Drug Products<sup>6</sup> and the FDA Points to Consider Document.<sup>7</sup> Clinical trials used to support the approval of antibacterial drugs from this point forward were generally designed as “equivalence” trials that were essentially noninferiority trials. The documents described the criteria to demonstrate “equivalence”, which stated in general that the two-sided 95% confidence interval of the difference in primary endpoint could not be greater than 10% to 15%. The “equivalence” trial is similar to the noninferiority trial, except that the noninferiority trial focuses on the lower bound of the two-sided 95% confidence interval of the difference to establish a degree of confidence that a test drug is not inferior to a control drug.

To illustrate the types of noninferiority clinical trials that were used to support approvals in the 1990s, examples from three antibacterial drugs are described below.

The first example is an antibacterial drug approved in the 1990s. The following two trials were included in the New Drug Application (NDA) to support the indication of “acute bacterial sinusitis”.

- One randomized, active-controlled trial enrolled 542 subjects with radiographic evidence of acute sinusitis (e.g. air-fluid levels, opacification, or mucosal thickening) and at least two clinical signs referable to a subject’s sinus infection. The primary efficacy endpoint was the investigator-assessment of resolution of sinusitis, defined as improvement or absence of the clinical signs and symptoms of sinus infection. Approximately 89% of subjects randomized to receive the test antibacterial drug achieved resolution of sinusitis compared to approximately 89% of subjects randomized to receive the control antibacterial drug. The lower bound of the two-sided 95% confidence interval of the difference was approximately -12%, which met the trial’s pre-specified difference of not

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<sup>6</sup> [Beam TR Jr](#), [Gilbert DN](#), [Kunin CM](#). General guidelines for the clinical evaluation of anti-infective drug products. Infectious Diseases Society of America and the Food and Drug Administration. Clin Infect Dis. 1992 Nov;15 Suppl 1.

<sup>7</sup> Guidance for Industry, *Clinical Development and Labeling of Anti-infective Drug Products*. October, 1992; revised 2/2001. Available at <http://www.fda.gov/cder/guidance/index.htm>



greater than -15%. Cultures of sinus aspirates were not obtained in the study. Approximately 25% of subjects randomized to the test drug experienced gastrointestinal adverse events in the study, in comparison to approximately 14% of subjects randomized to receive the control drug. The control antibacterial drug was approved in the 1980s for “treatment of sinusitis” on the basis of one active-controlled study of sinusitis, where 73% of subjects reported “improvement” compared to 68% on a control antibacterial drug that had been approved prior to 1980 for “treatment of respiratory tract infections”.

- A second randomized, active-controlled trial enrolled 497 subjects with radiographic evidence of acute sinusitis and at least two clinical signs referable to a subject’s sinus infection. Similar to the study above, the primary efficacy endpoint was the investigator-assessment of resolution of sinusitis. Approximately 89% of subjects randomized to receive the test antibacterial drug achieved resolution of sinusitis compared to 87% of subjects on the control antibacterial drug. The lower bound of the two-sided 95% confidence interval of the difference was approximately -4%, which also met the trial’s pre-specified difference of not greater than -15%. Cultures of sinus aspirates were not obtained in this study. Approximately 20% of study subjects randomized to the test drug experienced gastrointestinal adverse events, in comparison to approximately 16% of subjects randomized to the control drug. The control antibacterial drug was the same drug used as the control drug in the first study above.

This application included three other studies in patients with acute sinusitis. Two were randomized, active-controlled clinical trials that evaluated different treatment durations (7 days instead of 10 days) of the test antibacterial drug and included the same control antibacterial drug that was used in the above two trials. The study endpoints and results were similar to the above two trials. In addition, an open-label uncontrolled study that recorded clinical observations in patients with acute sinusitis was also included.

The second example is another antibacterial drug approved in the 1990s. The following two trials were included in the NDA for the indication of “treatment of acute otitis media”.

- One randomized, active-controlled trial enrolled 852 children ages 6 months to 12 years with signs and symptoms of acute otitis media. The primary efficacy measurement of success was “satisfactory remission” or absence of clinical signs and symptoms of otitis media after completion of therapy, as adjudicated by the investigator using clinical signs and patient symptom scores. Approximately 70% of patients randomized to the test antibacterial drug achieved an adequate clinical response compared to approximately 73% of patients randomized to the control antibacterial drug. The lower bound of the two-sided 95% confidence interval of the difference was approximately -14%, which met the trial’s pre-specified difference of not greater than -15%. Gastrointestinal adverse events were observed in approximately 20% of subjects treated with the test drug, most

often diarrhea. Among subjects treated with the control drug, approximately 38% experienced gastrointestinal adverse events. The control antibacterial drug was approved prior to 1980 for treatment of “infections of the ear, nose, and throat”.

- Another randomized, active-controlled trial enrolled 752 children ages 6 months to 12 years with signs and symptoms of acute otitis media. The design was nearly identical to the study above with the exception that tympanocentesis was not performed. Approximately 91% of patients randomized to receive the test antibacterial drug achieved a “satisfactory remission” or absence of clinical signs and symptoms of otitis media, compared to approximately 85% of patients randomized to receive the control antibacterial drug. The lower bound of the two-sided 95% confidence interval of the difference was approximately -10%, which also met the trial’s pre-specified criteria of not greater than -15%. Gastrointestinal adverse events were also the most commonly observed adverse events, with approximately 19% of subjects in the test drug group in comparison to approximately 22% of subjects in the control drug. Diarrhea was the most common gastrointestinal adverse event. The control antibacterial drug was approved prior to 1980 for treatment of “infections of the ear, nose, and throat”.

The third example is an antibacterial drug also approved in the 1990s. The following two trials were submitted in the NDA to support the indication for the treatment of “acute exacerbation of chronic bronchitis”.

- One randomized, active-controlled trial enrolled 373 subjects experiencing an acute exacerbation of chronic bronchitis defined as worsening cough and a change in character of sputum production. The primary efficacy endpoint was the investigator assessment as cured, improved, or failed therapy at one week after completion of therapy. Approximately 50% of the study patients were considered to be not evaluable in the efficacy analyses because of alternative diagnoses (e.g., bacterial pneumonia), non-adherence to study drug treatment, or cultures did not demonstrate a bacterial pathogen. In the group randomized to receive the test antibacterial drug, 97 out of 103 evaluable subjects (approximately 94%) achieved clinical improvement of “improved” or “cured”, while in the group randomized to receive the control antibacterial drug, 77 out of 89 subjects (approximately 87%) achieved clinical improvement. The point estimate of clinical improvement was higher for the test antibacterial drug, however, the two-sided 95% confidence intervals of the difference included zero and the lower bound of the 95% confidence interval met the trial’s pre-specified margin of not greater than -10%. Gastrointestinal adverse events were the most frequently observed adverse events, and occurred in approximately 17% of study subjects receiving the test drug and approximately 15% of subjects receiving the control drug. The control antibacterial drug was approved prior to 1980 for “respiratory tract infections”.

- A second randomized, active-controlled trial enrolled 492 subjects experiencing an acute exacerbation of chronic bronchitis defined as worsening cough and a change in character of sputum production. The primary efficacy endpoint was the investigator assessment as “cured”, “improved”, or “failed therapy” at one week after completion of therapy. Approximately 43% of study patients were considered to be not evaluable in the efficacy analyses for similar reasons listed in the trial above. In the group randomized to receive the test antibacterial drug, 129 out of 134 evaluable subjects (approximately 96%) achieved clinical improvement of “improved” or “cured”, while in the group randomized to receive the control antibacterial drug, 137 out of 147 subjects (approximately 93%) achieved clinical improvement. The lower bound of the two-sided 95% confidence interval of the difference was approximately -7% and met the trial’s pre-specified margin of not greater than -10%. Gastrointestinal adverse events were the most frequently observed adverse events, and occurred in approximately 26% of study subjects randomized to receive the test drug in comparison to approximately 30% of subjects randomized to receive the control drug. The control antibacterial drug was approved a decade earlier for treatment of “acute bronchitis” on the basis of four active-controlled clinical studies, which included some patients with acute exacerbation of chronic bronchitis. The control antibacterial drugs used in those four studies were approved prior to 1980 for “respiratory tract infections”.

Antibacterial drugs approved before the 1980s were, in general, used as the control antibacterial drugs in noninferiority trials. Because placebo-controlled trials were not used as a basis for the approval of those drugs, a treatment effect of the control antibacterial drugs over placebo had not been clearly established. Thus, these active-controlled studies may not provide a reliable means to evaluate efficacy of the newer antibacterial drugs for treatment of acute bacterial sinusitis (ABS), acute bacterial otitis media (ABOM), and mild to moderate acute bacterial exacerbation of chronic bronchitis in patients with chronic obstructive lung disease (ABECB-COPD). As a treatment effect of control antibacterial drug cannot be clearly established in these indications, we no longer recommend non-inferiority trials for ABS, ABOM, and mild to moderate ABECB-COPD.

We briefly illustrate the total amount of phase 3 clinical data that were submitted in a New Drug Application (NDA) for FDA review. This example was taken from an NDA submitted in the 1990s, approximately 20 years ago. Two randomized controlled clinical trials of the investigational drug compared to an active-control drug were conducted in each of the following infectious diseases: 1) acute sinusitis; 2) acute exacerbation of chronic bronchitis; 3) community-acquired pneumonia; 4) complicated skin and skin structure infections; 5) uncomplicated skin and skin structure infections; and, 6) complicated urinary tract infections and acute pyelonephritis. Approximately 5,900 patients comprised the safety and efficacy database for the phase 3 clinical trials submitted for review in this NDA submission.

### 3. Advances in Scientific Knowledge that Affected Antibacterial Drug Development

An important recognition is the change in the approach to evaluating new drugs for treatment of ABS, ABOM, and mild-to-moderate ABECB-COPD. The treatment effect is small, at best, for these “milder” infectious diseases such that the noninferiority trial is not recommended. The guidance documents for ABS, ABOM, and ABECB-COPD recommend superiority trials for the demonstration of efficacy. The issues with clinical trials in ABS, ABOM, and mild-to-moderate ABECB-COPD were discussed at several AIDAC meetings in the past.<sup>8</sup>

Therefore, antibacterial drug development using a noninferiority trial design would now typically enroll patients with a greater severity of disease. Over the past several years, we have conducted evaluations of the Historical Evidence for Sensitivity to Drug Effects, or HESDE, for several serious infectious diseases. Through this work, we have been able to identify clearly established treatment effects that form the basis for a scientifically sound noninferiority trial design, for example acute bacterial skin and skin structure infection (ABSSSI), community-acquired bacterial pneumonia (CABP), complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), or hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP).<sup>9</sup> The justifications for the noninferiority trial design and selection of a noninferiority margin are included in each guidance document.

Conducting clinical trials in patients with serious bacterial infectious diseases can be challenging for a number of different reasons. The need for urgent administration of antibacterial drug therapy was generally recognized as important for these more serious infectious diseases but

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<sup>8</sup> On several occasions, FDA Advisory Committees have addressed issues regarding clinical development of antibacterial drugs that are seeking indications for infections that are potentially self-limited and are based on the demonstration of noninferiority to an approved antibacterial drug. In 2002, an FDA Anti-Infective Drugs Advisory Committee discussed clinical studies of antibacterial drugs for treatment of ABECB; the committee recommended placebo-controlled studies for subjects who are not severely ill in order to demonstrate efficacy. Also in 2002, the committee considered clinical trial designs of antibacterial drug products for treatment of ABOM. In general, the committee favored clinical trial designs that would be more informative for evaluation of antibacterial drugs for treatment of ABOM including the incorporation of a placebo control. In 2003, the FDA convened an advisory committee to discuss the trial designs for demonstration of efficacy for an antibacterial drug for the treatment of ABS. The committee recommended that studies be designed to show superiority of the test antibacterial drug, e.g., through placebo-controlled clinical studies. A September 2006 meeting of the Anti-Infective Drugs Advisory Committee discussed an antibacterial drug for consideration of approval based on an active-controlled noninferiority study for the indication of ABS; the committee favored not approving the product because the noninferiority study design did not provide an adequate demonstration of efficacy. In December 2006, the same advisory committee discussed the FDA-approved indications for Ketek® (telithromycin), which were approved on the basis of active controlled trials designed to show noninferiority. The committee recommended removal of two indications, ABS and ABECB, in part because it was not possible to reliably show the effect of the active drug for these two indications on the basis of the noninferiority clinical trial design. The Ketek® (telithromycin) product label was subsequently amended to remove the indications for ABS and ABECB.

<sup>9</sup> See the CDER Clinical/Antimicrobial guidance web page at:  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064980.htm>

more recently has been carefully described for many infectious diseases. For example, in-hospital mortality was reduced when antibacterial drugs were administered within 4 hours to patients who had community-acquired bacterial pneumonia.<sup>10</sup> Patients often receive antibacterial drug therapy promptly as standard of care, and are then considered for enrollment into clinical trials. The administration of an effective antibacterial drug before the patient is enrolled in the trial may obscure the effect of an antibacterial drug under study, which is an important concern for the noninferiority trial design. Another challenge is the severity of the acute illness, which may make obtaining informed consent and performing other trial enrollment procedures rapidly more difficult (e.g., acute delirium in the setting of an acute infection). Finally, there is often diagnostic uncertainty when the patient first presents with an infectious disease, and it may take time to identify the specific bacteria causing the infection and to evaluate its in vitro antibacterial susceptibility testing. Until the bacteria can be identified and evaluated, it may be necessary to administer other empirical antibacterial drug therapy along with the investigational drug under study. There are significant challenges to obtain informed consent and to conduct other enrollment procedures so that patients are randomized and receive urgently the clinical trial antibacterial drugs, without need for administration of other antibacterial drugs.

#### **4. Summary of Meetings, Workshops, and Activities Related to Antibacterial Drug Development**

Recent workshops were convened to bring together thought leaders and experts in infectious diseases to discuss clinical trial design issues in general and in certain site-specific infectious diseases. Valuable discussions from these FDA-sponsored and FDA-cosponsored workshops were helpful to formulate topics for AIDAC discussions and issuance of draft indication-specific guidance documents over the past several years. The Office of Antimicrobial Products and the Division of Anti-Infective Products have engaged several outside groups to advance the science of clinical trials for antibacterial drugs. The Biomarkers Consortium of the Foundation for the National Institutes of Health identified well-defined and reliable interim endpoints for clinical trials in CABP and in ABSSSI. The Clinical Trials Transformation Initiative works on increasing efficiency of clinical trials, including their work on clinical trials in HABP/VABP, as well as holding workshops on statistical issues in antibacterial drug development. The Engelberg Center for Health Care Reform at the Brookings Institution addresses overarching issues related to antibacterial drug development.

The following are examples and dates of different workshops and AIDAC discussions that have taken place:

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<sup>10</sup> Houck PM, Bratzler DW, Wato N, Allen M, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med* 2004;164:637-644.

- Issues in the Design of Clinical Trials for Antibacterial Drugs for Community-Acquired Pneumonia (CABP); January 17 & 18, 2008<sup>11</sup>
- Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia (HABP) and Ventilator-Associated Pneumonia (VABP); March 31 & April 1, 2009<sup>12</sup>
- Issues in the Design and Conduct of Clinical Trials for Infectious Disease Indications; August 2 & 3, 2010
- The November 3 & 4, 2011 AIDAC meetings on clinical trial designs and endpoints for HABP/VABP and CABP

## 5. Summary of Current Issues in Streamlined Antibacterial Drug Development Programs

Given the challenges associated with the development of new antibacterial drugs for each of several different body sites, it is no longer feasible to expect the type of phase 3 drug development program that took place approximately 20 years ago, in which over 5,000 patients were enrolled into multiple clinical trials. We are mindful of these challenges in addition to the current economic framework for new antibacterial drug development<sup>13</sup>, and thus we are exploring different approaches that may help streamline antibacterial drug development, especially for drugs that could address an unmet medical need, while still maintaining our regulatory mandate for the demonstration of safety and efficacy of new drugs.

These efforts have helped to identify trial design considerations for a streamlined development program. We described clinical development and trial design considerations in the draft guidance document, *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases*.<sup>14</sup> The general topic areas are summarized in the

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<sup>11</sup> See Workshop on issues in the design and conduct of clinical trials of antibacterial drugs in the treatment of community-acquired pneumonia. *Clinical Infectious Diseases* 2008;47 (Suppl 3): S105-S265.

<sup>12</sup> See Workshop on issues in the design of clinical trials for antibacterial drugs for hospital-acquired pneumonia and ventilator-associated pneumonia. *Clinical Infectious Diseases* 2010;51 (Suppl 1): S1-S171.

<sup>13</sup> See the report, *Analytic Framework for Examining the Value of Antibacterial Products*, prepared by Eastern Research Group, Inc. under contract to the Assistant Secretary for Planning and Evaluation at the U.S. Department of Health and Human Services. This report can be accessed at:  
[http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt\\_antibacterials.cfm](http://aspe.hhs.gov/sp/reports/2014/antibacterials/rpt_antibacterials.cfm)

<sup>14</sup> See the draft guidance at:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM359184.pdf>

following sections to this document. We seek advice and discussion on the type and amount of data collected during antibacterial drug development for therapies for patients with unmet medical need for the treatment of serious bacterial diseases.

The AIDAC will be asked to discuss the current issues pertaining to the development of antibacterial drugs for treatment of serious infectious diseases in patients who have an unmet medical need. The following summary information provides some background information for the discussion.

a. Overview of the present regulatory landscape for streamlined drug development

Antibacterial drugs approved on the basis of a streamlined clinical development program must still meet the statutory standards for safety and effectiveness (section 505(d) of the Food, Drug, and Cosmetic Act). For effectiveness, the standard is substantial evidence based on adequate and well-controlled clinical investigations (section 505(d)(5) of the Act). As noted previously, regulations promulgated in 1986 defined the characteristics of an adequate and well-controlled study (21 CFR §314.126(b)). For safety, the standard is having sufficient information to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling (section 505(d)(1) of the FD&C Act). However, safety is inherently a risk-benefit consideration, such that drugs with substantial benefits, such as fulfilling an unmet medical need, can have greater toxicity and still have benefits that outweigh the risks of the drug (see 21 CFR §312.80, subpart E, *Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses*)<sup>15</sup>. Furthermore, Section 115(a) of the Modernization Act allowed for data from one adequate and well-controlled clinical investigation, plus confirmatory evidence, to establish effectiveness. These regulations, along with guidance for industry documents such as *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, describe the FDA's flexibility within these statutory requirements.<sup>16</sup>

b. Nonclinical evaluations of new antibacterial drugs

Nonclinical data can provide important information about features of the drug that contributes to treatment of patients with unmet medical need. The mechanism of action of the drug should be elucidated and whether mechanisms of resistance to other drugs affect the drug's activity. From

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<sup>15</sup> 21 CFR §312.80 states the following: “*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>16</sup> See CDER's Guidance Webpage, found at: <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf>

a representative sample of target bacterial pathogens, including bacterial pathogens that have resistance to other drugs, the in vitro activity should be described, including the tentative in vitro minimum inhibitory concentration (MIC) of an investigational drug. Evidence of the drug's ability to achieve appropriate levels in relevant tissue sites should be examined in appropriate animal models of infection. The cumulative amount of information should be available to estimate a target value of the PK/PD index that is associated with efficacy in the animal models. To the extent that clinical evaluations will likely be "streamlined" or smaller to demonstrate the statutory requirements for safety and efficacy, this type of nonclinical information in a streamlined clinical development program would be particularly important for an overall evaluation of efficacy and safety of an investigational drug.

c. PK and PD evaluations in streamlined drug development programs

The pharmacokinetic (PK) and pharmacodynamics (PD) data will be an important component of a streamlined development program. Information about the distribution of the drug to the site of action is relevant information to initiate clinical development. For example, a drug's distribution in epithelial lining fluid provides information regarding a drug's potential to treat bacterial pneumonia. PK information from humans in early clinical development, along with PK/PD (e.g., "exposure-response") data from animal models of infection, can provide important information that contributes to dose selection for later stage clinical development. Sparse sampling strategies from patients enrolled in clinical trials can help address concerns about efficacy or safety that arise and help describe the effects of intrinsic and extrinsic factors on PK/PD. Patients with serious bacterial infections with an unmet medical need often have important comorbidities, notably renal or hepatic impairment, and, therefore, an increased likelihood of alterations in PK. Characterization of PK in such patients is integral to a streamlined drug development program.

d. Clinical investigations in a streamlined drug development program

The FDA issued draft guidance in 2013 and has reviewed the comments to the docket in response to the draft guidance. In the sections below, we summarize some of the current issues in streamlined drug development programs where the AIDAC discussion and comments will be valuable.

### Single Body-Site Noninferiority Trials

An approach to antibacterial drug development based on showing efficacy in single body site noninferiority trials is still a viable option. There has been a considerable effort focused on noninferiority trial designs for each of a number of different body site infections that result in scientifically sound and feasible trials.<sup>17</sup> Three new antibacterial drugs were approved for

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<sup>17</sup> See the CDER Clinical/Antimicrobial guidance document webpage at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064980.htm>



ABSSSI in 2014 (tedizolid, dalbavancin, and oritavancin), based on the noninferiority trial design.

The efficacy of an investigational drug intended to treat serious bacterial diseases in patients with an unmet medical need can be established on the basis of a noninferiority trial in a population of patients who have treatment options for their serious bacterial disease. The trial population should include patients with severity of illness and/or comorbid conditions that are similar to those of patients who have an unmet medical need to have a finding of safety and efficacy that can be relevant to the patient population with unmet medical need (i.e., patients with infections caused by bacteria resistant to other available antibacterial drugs).<sup>18,19,20</sup>

If the antibacterial drug would be indicated for use only for patients who have limited or no treatment options, the characterization of efficacy in a noninferiority trial could be based on a larger than usual noninferiority margin that still establishes effectiveness (i.e.,  $M_2$  could be closer to  $M_1$  than is usual). The “streamlined” approach is the smaller sample size for the clinical trial with a larger than usual noninferiority margin that could result in completion of a trial in a shorter period of time.

An additional clinical trial in patients with an unmet medical need should supplement the safety and efficacy data from the noninferiority trial because usually there will be few, if any, patients who have an unmet medical need in the noninferiority trial.<sup>21</sup> The additional clinical trial can be conducted in patients with the specific type of infection studied in the noninferiority trial as well as other types of infections of comparable or greater disease severity. Ideally, a randomized active-controlled trial is the best option, if active control therapy is feasible and ethical, because then comparative safety and efficacy evaluations can be performed. Experience has shown that having a randomized comparator group can be particularly important for interpreting safety data from the trial (in small trials that enroll acutely ill patients, having a comparator group can help

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<sup>18</sup> Patients with unmet need may have greater comorbidities, altered pharmacokinetics, or disease severity that affect treatment effect and patient outcomes. Enrolling patients in the noninferiority trial with these characteristics should increase the generalizability to similar populations of patients who have unmet need.

<sup>19</sup> A hierarchical nested noninferiority/superiority analysis can be considered if a sufficient number of patients 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.

<sup>20</sup> If the investigational drug is shown to be effective in treating a particular type of infection caused by certain bacteria, it should remain effective as long as the bacteria causing the infection are susceptible to the investigational drug. If these bacteria are susceptible to the investigational drug, that they are resistant to other antibacterial drugs is generally not a determinant factor in the efficacy of the investigational drug. As noted, it is important to enroll patients with severity of illness and/or comorbid conditions comparable to patients with unmet medical need so that results are generalizable.

<sup>21</sup> See, for example, the “Tier B” paradigm in Rex JH, BI Eisenstein, J Adler, et al., 2013, A Comprehensive Regulatory Framework to Address the Unmet Need for New Antibacterial Treatments, *Lancet Infect Dis*, 13(3):269-273.

in evaluating adverse events that may represent background adverse events in this ill population). This trial does not have to be powered for inference testing, although a finding of superiority is always obviously an interpretable result.

In this second trial, information should be collected on patient comorbidities, disease severity, and pharmacokinetics, with comparisons to the patient population in the noninferiority trial.

In addition, in our body site indication-specific guidance documents, we outline an approach that one successful noninferiority trial in a single body site and one successful noninferiority trial in a different body site can provide evidence of efficacy for treatment of both body site infectious diseases.

Although we would welcome additional comments and discussion about the role of a body site noninferiority trial, we remain confident that this approach is able to demonstrate safety and effectiveness of new antibacterial drugs in current and future development.<sup>22</sup>

### Superiority Clinical Trials

An investigational drug can be compared to best-available active control therapy in a single randomized controlled superiority trial. Sponsors should discuss with the FDA the type of trial design (e.g., a trial enrolling patients who have a particular type of infection (e.g., ventilator-associated bacterial pneumonia) or who have different types of infection (e.g., ventilator-associated bacterial pneumonia and complicated intra-abdominal infection) and inferential statistical evaluations for a finding of superiority.

There may not be sufficient experience to identify a noninferiority margin for the best available active control, but it is likely that it has an effect greater than no treatment or “placebo”. Given the likelihood of an active control that has some treatment benefit, it may be difficult to show unequivocal superiority for the investigational drug. In this setting where there is some treatment benefit of the active control, it may be an appropriate consideration to use a less stringent statistical finding for superiority to demonstrate efficacy of the investigational drug. For example, a trial may be powered for a finding of superiority based on a one-sided significance level equal to 0.05. Thus, an efficacy finding based on this less stringent evidence of superiority over the active control provides evidence of efficacy that is actually based on a finding of superiority to no treatment or “placebo”.

A superiority trial design can be used to evaluate an antibacterial drug with activity against a single species (or a few species) of bacteria. A sufficient number of patients for enrollment into a trial of a particular type of infection (e.g., HABP/VABP) may not be available. Patients with

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<sup>22</sup> Nambiar S, Laessig K, Toerner J, Farley J, Cox E. Antibacterial drug development: challenges, recent developments, and future considerations. *Clinical Pharmacology and Therapeutics* 2014;96(2):147-149.

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.

A superiority clinical trial design that relies on an external control population may be appropriate to evaluate efficacy when the untreated morbidity and/or mortality is high and does not vary widely in the patient population with unmet medical need, and the effect of the investigational drug in an unmet medical need population is expected to be large.<sup>23</sup> For an externally controlled trial, the control patients should be as similar as possible to the population expected to receive the investigational drug. Patients should have been treated in a similar setting and in a similar time frame, except with respect to the investigational drug therapy. For sponsors considering an externally controlled trial, we recommend randomizing at least a small number of patients to the active control (e.g., through disproportionate randomization of 4:1), if feasible and ethical based on an active control considered to be best-available therapy. This will allow for an assessment of the comparability of the external control to the trial population. Frequentist and Bayesian statistical methods can then be used to combine external control data with data from the patients randomized to the active control in assessing differences between treatment groups for the primary comparison.

#### Nested noninferiority/superiority clinical trials

Patients with and without unmet medical need can be included in a nested, active-controlled noninferiority/superiority trial design. Patients should be randomized to investigational drug or control drug before the availability of the results of antibacterial drug susceptibility testing of the bacteria causing the patient's infection because of the time required for results from susceptibility testing to become available using current technologies. The trial should include provisions for adjusting the control regimen to provide standard-of-care treatment for patients who are found to have resistant bacterial isolates at baseline. It is essential that adequate procedures be in place to protect patients enrolled in this trial from avoidable exposure to less effective therapy.

In this trial design, the first step should be to demonstrate noninferiority of the investigational drug to the control treatment in the population of patients who have a baseline bacterial isolate susceptible to the control drug. The second step should be to evaluate superiority in patients subsequently confirmed to be infected with a baseline bacterial isolate resistant to the control drug.<sup>24</sup> This type of hierarchical nested design does not require any multiplicity adjustments to control the overall type I error rate.<sup>25</sup>

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<sup>23</sup> See ICH E10.

<sup>24</sup> 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.

A finding of efficacy could be based on a demonstration of noninferiority to an effective comparator in the population of patients with a baseline bacterial isolate susceptible to the comparator drug. After a finding of noninferiority has been demonstrated, as noted earlier, demonstration of superiority in the population of patients with a baseline bacterial isolate resistant to the comparator drug can be tested as an option. Given the sequential nature of the preplanned testing, a noninferiority test followed by testing for superiority, there would be no statistical penalty for the superiority evaluation.

### Multiple Body-Site Infection Trials

In general, multiple body-site infection trials should be designed as superiority trials in patients with an unmet medical need. In addition, these trials should be considered when factors preclude the enrollment of patients in trials of infections at a single body site; for example, an antibacterial drug with activity against a single species (or a few species) of bacteria. It is also important that adequate information about the distribution of the drug to the site of action be evaluated before selection of the body sites to be pooled.

There may be several options to consider for a primary efficacy endpoint for this trial design. One option is to use different clinical efficacy endpoints based on each body site infection. For example, patients who have complicated intra-abdominal infections would be evaluated on the clinical success outcome at day 28 after randomization, and patients who have complicated urinary tract infections would be evaluated on the responder outcome at 7 days after completion of antibacterial drug therapy. Thus, each patient would be counted as a *success* or *failure*, depending on the outcome specific to each body site infection. 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 streamlined development program that includes a trial enrolling patients with infections at different body sites may have reduced capacity to detect relative deficits in performance of an antibacterial drug in some body sites compared to others. There have been several recent instances where unexpected results from clinical trials revealed deficits in the performance of an antibacterial drug.<sup>26</sup> Trials that enroll patients with infections at different body sites associated with similar severity and comorbid conditions are more likely to be interpretable.

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<sup>25</sup> 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, *Statistics in Medicine*, first published online 23 June 2014, DOI: 10.1002/sim.6233.

<sup>26</sup> See the following: FDA Statement on recently terminated clinical trial with Doribax (doripenem): Safety Announcement: [01-05-2012] (available at <http://www.fda.gov/Drugs/DrugSafety/ucm285883.htm>); FDA Drug Safety Communication: FDA warns of increased risk of death with IV antibacterial Tygacil (tigecycline) and approves new Boxed Warning: Safety Announcement: [9-27-2013] (available at <http://www.fda.gov/drugs/drugsafety/ucm369580.htm>); Pertel PE, P Bernardo, C Fogarty, P Matthews, et al., 2008,

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 body site infections that have different severity and associated comorbid conditions; for example, a trial that enrolls patients with complicated urinary tract infection and ventilator-associated bacterial pneumonia. Modeling approaches provide a measure of internal consistency of treatment effect among the subgroups of each body site.

Some discussions have included an uncontrolled trial in which all enrolled patients who have unmet medical need are treated with the investigational drug. In this situation, an external control or historical control could be used for inferential statistical testing. However, as noted in 21 CFR §314.126(a)(2)(v), “because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances”, such as “diseases with high and predictable mortality”. The ICH E 10 guidance, *Choice of Control Group and Related Issues in Clinical Trials*<sup>27</sup>, notes that results of externally controlled trials are likely to be more persuasive when the outcome in the investigational drug group is markedly different from the external control group and has a high level of statistical significance. An overview of contemporary reports suggest that mortality associated with infections caused by bacteria that are resistant to all antibacterial drugs is approximately 40% for a survival rate of 60%. For an investigational drug to show effectiveness against an external control, the superiority of the investigational drug over an external control should be persuasive. Unless survival rates are approximately 80% or higher in the unmet medical need population of patients receiving the investigational antibacterial drug, a survival rate of 60% may limit the ability to show persuasive evidence of superiority based on an external or historical control.

At this point in time, the use of the noninferiority trial design may not meet the scientific standards for a multiple body-site trial because a reliable treatment effect of the active control therapy has not been elucidated. As noted above, there are differences in the efficacy outcome assessments based on each individual infectious disease. In addition, patients should receive the standard of care as the active control, but the standard of care antibacterial drug therapy and its effectiveness may differ substantially among trial sites because of differences in antibacterial susceptibility profiles of bacterial pathogens among the sites. Thus, a finding of superiority in a multiple body-site trial is the preferred option at this point in time. If a treatment effect can be elucidated by additional work in this area, a possible approach is to construct a noninferiority trial design (i.e., an investigational drug is not worse than the control therapy by a prespecified

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Effects of Prior Effective Therapy on the Efficacy of Daptomycin and Ceftriaxone for the Treatment of Community-Acquired Pneumonia, Clin. Infect. Dis., Apr 15, 46(8):1142-51, doi: 10.1086/533441.

<sup>27</sup> See the CDER guidance page at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073139.pdf>

amount), but the point estimate of success of the investigational drug could be expected to be greater than the control. The finding of noninferiority based on a point estimate of the effect of the investigational drug better than the active control would offer a conclusion that the investigational drug is better than placebo or no antibacterial drug treatment. This approach would require further work and discussion.

It is important to consider the possibility for disparate outcomes for each different body site infection. The clinical experiences with daptomycin for treatment of community-acquired pneumonia, and doripenem or tigecycline for treatment of hospital-acquired/ventilator-associated bacterial pneumonia, highlight the potential for disparate outcomes when considering a particular body site infection.<sup>28</sup>

Finally, while enrolling patients with any one of several body site infections is a clinical trial design that harkens back to trials used in the 1960s, a multiple body-site trial today would have a statistical analysis plan that may include Bayesian approaches or a combination of frequentist and Bayesian statistical approaches, that account for the differences in disease severity and endpoints among each body site of infection. Information about the distribution of the drug to the site of action of relevant body sites is also an important consideration. The results of trial enrolling across multiple body sites of infection should have a finding that supports an investigational drug's safety and effectiveness.

#### Other Considerations in a Streamlined Antibacterial Drug Development

Another approach has been the enrollment of patients with infections caused by one bacterial species (e.g., *Pseudomonas aeruginosa*). For such a development program, the identification of a rapid diagnostic that accurately and reliably detects the particular pathogenic bacteria may be a necessary first step for this approach to be truly viable. Thus, once a rapid diagnostic is available, sponsors may pursue drug development using the aforementioned streamlined programs, such as a trial enrolling patients who have infections at any one of a number of different body sites. While the evaluation of an indication for treatment of a specific bacterial pathogen harkens back to the DESI reviews of antibacterial drugs approved before 1962, this approach today should have robust and pre-specified statistical analyses and adequate information about the distribution of the drug to the site of action at the relevant body sites. The results of such a trial should have an efficacy finding that supports an investigational drug's effectiveness.

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<sup>28</sup> Silverman JA, Mortin LI, VanPraagh A, et al. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *J Infect Dis* 2005;191:2149-2152; Kollef MH, Chastre J, Clavel M, et al. A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. *Critical Care* 2013;16:R218; DOI <http://ccforum.com/content/16/6/R218>; Freire AT, Melnyk V, Kim MJ, et al. Comparison of tigecycline with imipenem/cilastatin for treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis* 2010;68(2):140-151.

If a new  $\beta$ -lactamase inhibitor drug is combined with an approved  $\beta$ -lactam antibacterial drug, FDA can rely on the findings of safety and effectiveness for the  $\beta$ -lactam antibacterial drug, under the 505(b)(2) pathway. Nonclinical data should demonstrate the activity of the combination from in vitro studies and animal models of infection. Limited efficacy data and safety data with the use of the new  $\beta$ -lactamase inhibitor plus the  $\beta$ -lactam antibacterial drug should be provided. Unless the drug development program contains robust clinical efficacy data, the labeling would generally be limited for use only when there are few or no other options for treatment.

The “Tiered Approach” was presented as a spectrum of regulatory approval pathways.<sup>29</sup> The Tier A approach consisting of indication-specific noninferiority clinical trials is an acceptable and traditional approach, but does not represent a streamlined approach to drug development. The Tier B approach is a streamlined approach consisting of one phase 3 body site trial with inference testing demonstrating effectiveness and safety in the one body site, plus other descriptive studies in patients receiving the new investigational drug; this approach may fulfill FDA’s requirements to demonstrate safety and effectiveness. Tier C is an approach consisting of small comparative and/or noncomparative studies without statistical inference testing, and may not be sufficient to fulfill FDA’s requirements for the demonstration of safety and effectiveness. The Tier D approach is an animal rule approach; however, clinical trials of investigational antibacterial drugs can be conducted in human populations and the animal rule may not be an applicable regulatory paradigm in this setting.

Product labeling is another consideration in streamlined drug development plans. FDA regulations have specific requirements on the content and format of labeling for human prescription drugs (21 CFR §201.57). For the Clinical Studies section of product labeling, any clinical study that is discussed in prescription drug labeling that relates to an indication for or use of the drug must be adequate and well-controlled as described in 21 CFR §314.126(b) and must not imply or suggest indications or uses or dosing regimens not stated in the "Indications and Usage" or "Dosage and Administration" section (21 CFR §201.57(c)(15)).

The labeled indications for drugs approved under a streamlined development program should reflect the patient population for which the drug is approved. Examples of potential labeling indications include the following:

*Drug X is indicated, for the treatment of infection Y caused by the following susceptible microorganism(s) [e.g., bacterium A, bacterium B, bacterium C...]*

*Drug X has been approved for use in patients with infection Y where limited or no alternative therapies are available.*

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<sup>29</sup> Rex JH, BI Eisenstein, J Adler, et al., 2013, A Comprehensive Regulatory Framework to Address the Unmet Need for New Antibacterial Treatments, Lancet Infect Dis, 13(3):269-273.

In summary, the history of antibacterial drug development spans more than seven decades. A review of the past several decades of antibacterial drug development provides an insight into issues that are encountered in a streamlined antibacterial drug development program. The drug development programs of the 1960s and 1970s generally provided information from several hundred patients enrolled in a “multiple body site” study. Based on scientific advances in the understanding of body site infectious diseases and clinical trial designs, the drug development programs of the 1990s provided information from patients enrolled in trials of individual body sites of infection. Today, the many challenges facing antibacterial drug development may not be able to support a drug development program in which several thousand patients are enrolled in many clinical trials. However, a streamlined drug development program may help to address some of these challenges and provide safe and effective antibacterial drugs for patients with an unmet medical need.



## 6. DRAFT Discussion Points for the Committee

1. Please discuss the acceptability from a clinical perspective of a streamlined development program that has greater uncertainty about the safety and efficacy of a new drug because of the smaller size of the clinical studies.
2. Please discuss the following options for trial designs for streamlined development programs:
  - a. Non-inferiority trials
    - Non-inferiority trials at a single body site of infection (e.g., cUTI, cIAI) using larger than usual non-inferiority margins (e.g., M2 is closer to M1 than is usual in traditional development programs)
  - b. Superiority trials
    - Pooling across different body sites of infection
    - Selection of the control group for inference testing (e.g., best-available therapy, external control)
3. Please discuss trial design options for a product that has a spectrum of activity limited to one or two particular microorganisms (e.g., *Pseudomonas aeruginosa*, *Acinetobacter baumannii*).
4. Please discuss the acceptability of a smaller safety database (e.g., 300 – 400 patients exposed to the investigational drug at the dose and duration of therapy).