Guidance for Industry

Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment

DRAFT GUIDANCE

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

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Guidance for Industry[1]
Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment

I. INTRODUCTION

The purpose of this guidance is to assist sponsors and investigators in the clinical development of drugs for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP).[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for treatment of HABP and VABP. This draft guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective Products, pharmaceutical sponsors, the academic community, and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.[3] This guidance was prepared with the general understanding that a noninferiority trial design evaluating patients who have HABP/VABP would be used to demonstrate effectiveness.

This guidance revises the draft guidance for industry *Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment* issued in November 2010. This guidance includes revisions to the primary efficacy endpoints, the enrollment criteria, the suggested primary efficacy analysis populations, and the noninferiority margin justification.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical*

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

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

[3] In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of their drug product.

Principles for Clinical Trials and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[4]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

HABP and VABP by definition occur in hospitalized patients. A hospital stay of 48 hours or more will place patients at risk for colonization and potential infection with a variety of gram-positive and gram-negative bacteria. Examples of etiologic pathogens of HABP/VABP include gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus*, gram-negative Enterobacteriaceae such as *Klebsiella pneumoniae*, and other gram-negative aerobic bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter* species.

Clinical trials of an investigational drug for the treatment of HABP/VABP pose a number of different challenges (Sorbello, Komo, et al. 2010). The FDA has convened a number of public discussions on the topics of trial designs and endpoints for evaluation of antibacterial drugs for the treatment of HABP/VABP.[5]

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

New antibacterial drugs being studied for HABP/VABP should have activity against implicated pathogens for HABP/VABP.[6]

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[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] Transcripts of the March 31 and April 1, 2009, workshop co-sponsored by the FDA and professional societies, *Clinical Trial Design for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia*, can be found at http://www.fda.gov/Drugs/NewsEvents/ucm169877.htm; see also the November 4, 2011, Anti-Infective Drugs Advisory Committee meeting that devoted the discussion to HABP/VABP — meeting transcripts can be found at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm242307.htm.

[6] See the guidelines from the American Thoracic Society (ATS) and the Infectious Diseases Society of America (ATS 2005), or other relevant publications, for descriptions of bacterial pathogens commonly identified in patients with HABP/VABP.

2. Drug Development Population

The intended clinical trial population is patients with HABP/VABP. HABP is defined as an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms such as fever or hypothermia, chills, rigors, cough, purulent sputum production, chest pain, or dyspnea, accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient hospitalized for more than 48 hours or developing within 7 days after discharge from a hospital.[7] Patients may experience acute respiratory failure and require mechanical ventilation for HABP (ventilated-HABP).

VABP is defined as an acute infection of the pulmonary parenchyma that is associated with clinical signs and symptoms such as fever or hypothermia, chills, rigors, purulent respiratory secretions, and increased oxygen requirements accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient receiving mechanical ventilation via an endotracheal (or nasotracheal) tube for a minimum of 48 hours.

3. Efficacy Considerations

A showing of superiority to a control drug in the treatment of HABP/VABP is readily interpretable as evidence of effectiveness.[8] Noninferiority trials are also interpretable and acceptable as evidence of effectiveness in the treatment of HABP/VABP (see the Appendix).[9]

A single adequate and well-controlled trial can provide evidence of effectiveness.[10] Sponsors should discuss with the FDA the independent confirmation that would be used to support the findings from a single trial in HABP/VABP (e.g., the results of a trial in another infectious disease indication).

4. Safety Considerations

In general, we recommend a preapproval safety database of approximately 500 patients. If the same or greater dose and duration of therapy for treatment of HABP/VABP were used in clinical trials for other infectious disease indications, the safety information from those clinical trials can be part of the overall preapproval safety database. For new drugs that have an important clinical benefit compared to existing therapies, a smaller preapproval safety database may be sufficient. Sponsors should discuss with the FDA the appropriate size of the preapproval safety database during clinical development.

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[7] Oral and nasotracheal bacterial flora may not return to normal flora within 4 to 6 weeks or longer after hospitalization. However, this guidance provides a definition of HABP that ensures clinical trial populations with bacterial pathogens most commonly identified in HABP and VABP, and may differ from other definitions of HABP used in treatment guidelines.

[8] See section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

[9] Ibid.

[10] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

5. Clinical Microbiology Considerations

Patients enrolled in a HABP/VABP trial should have a baseline respiratory specimen obtained for Gram stain and culture. In addition to defining the bacterial etiology for HABP/VABP, the Gram stain and culture are important considerations because they may be used to define analysis populations (see section III.B.11.a. Analysis populations) and to characterize the quality and findings of the respiratory specimen sent for culture. More specifically, the low-power microscopic view of the Gram stain can be used to ascertain the quality of the respiratory specimen, which helps to ensure that the respiratory specimen sent for culture does not represent oropharyngeal contamination (e.g., fewer than 10 squamous epithelial cells and greater than 25 neutrophils is an example of an adequate expectorated sputum specimen). In addition, a high-power microscopic view of the Gram stain can be used to characterize the general type of bacteria causing the pneumonia (e.g., a gram-positive or a gram-negative bacterial pathogen). When bacterial growth is obtained on culture of the respiratory specimen, in vitro susceptibility tests should be performed by using standardized methods unless otherwise justified.[11]

B. Specific Efficacy Trial Considerations

1. Trial Design

HABP/VABP trials should be randomized and double-blind, comparing the investigational drug with an active control drug. In general, they will be designed as noninferiority trials but a showing of superiority would of course be interpretable. Placebo-controlled trials are not ethically considered appropriate for this indication except when they are add-on superiority trials in which patients receive either placebo or investigational drug added to standard-of-care antibacterial drug treatment.

2. Trial Population

The trial population can consist of the following types of patients:

- Patients who have HABP only
- Patients who have VABP only
- Patients receiving mechanical ventilation (either VABP or ventilated-HABP)
- Patients who have either HABP (regardless of mechanical ventilation) or VABP

In the historical data evaluated (see the Appendix), a majority of patients in the trials received mechanical ventilation. Therefore, for an indication for treatment of HABP and VABP, the trial population should include approximately 50 percent of patients who have VABP.

A clinical severity scoring system can be used to identify a trial population consisting of patients who have a sufficient severity of illness.

[11] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute; see also the American Society for Microbiology, 2011, Manual of Clinical Microbiology, 10th edition.

3. Inclusion and Exclusion Criteria

Suggested inclusion and exclusion criteria are described in the following two bullet points:

- **Inclusion criteria.** Hospitalized patients who experience an acute deterioration in respiratory status will have HABP/VABP included as one of a number of different potential diagnoses. Inclusion criteria should be designed to select patients who have evidence of a diagnosis of HABP/VABP at baseline. Patients should have:

  At least one of the following clinical features:

  – New onset or worsening pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (e.g., respiratory rate greater than 25 breaths per minute), expectorated sputum production, or requirement for mechanical ventilation

  – Hypoxemia (e.g., a partial pressure of oxygen less than 60 millimeters of mercury while the patient is breathing room air, as determined by arterial blood gas (ABG) or worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO2/FiO2))

  – Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO2/FiO2) or needed changes in the amount of positive end-expiratory pressure

  – New onset of suctioned respiratory secretions

  Plus

  At least one of the following signs:

  – Documented fever (e.g., body temperature greater than or equal to 38 degrees Celsius)

  – Hypothermia (e.g., core body temperature less than or equal to 35 degrees Celsius)

  – Total peripheral white blood cell (WBC) count greater than or equal to 10,000 cells/cubic millimeter (mm^3)

  – Leukopenia with total WBC less than or equal to 4,500 cells/mm^3

  – Greater than 15 percent immature neutrophils (bands) noted on peripheral blood smear

Plus

A chest radiograph showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia

- **Exclusion criteria.** The following patients should be excluded from HABP/VABP clinical trials:

  – Patients who have known or suspected community-acquired bacterial pneumonia or viral pneumonia

  – Patients who have received effective antibacterial drug therapy for HABP/VABP for a continuous duration of more than 24 hours during the previous 72 hours (see section III.B.8., Prior Antibacterial Drug Therapy).

4. Randomization and Blinding

Patients should be randomized to treatment groups at enrollment. Randomization strategies other than 1:1 (e.g., 2:1 or 3:1 randomization of investigational drug to active control) for trials could be considered in certain situations, for example, to enhance the size of the safety database of the investigational drug. To the extent possible, the investigational antibacterial drug and the active control antibacterial drug should be administered in a double-blinded fashion. If there is a compelling reason for single-blind or open-label trial designs, efforts to minimize bias should be discussed with the FDA before trial initiation.

For trials in patients with HABP/VABP, it often may be the case that few patients are enrolled at each clinical center. In this case, consideration may be given to randomizing centers rather than individual patients as a means to simplify enrollment, with appropriate adjustments to the statistical analysis plan and informed consent procedures to accommodate cluster randomization. Cluster randomization may help enhance the efficiency of the enrollment process and enable prompt administration of antibacterial drug therapy within the context of the clinical trial, thus avoiding the potential confounding issue of administration of effective antibacterial drug therapy before enrollment (see section III.B.8., Prior Antibacterial Drug Therapy).

5. Specific Populations

The trials should include patients of both sexes and all races, and should include geriatric patients.[12] Sponsors are encouraged to begin discussions about their pediatric formulation and clinical development plan early in development because pediatric studies are a required part of the overall drug development program and sponsors are required to submit pediatric study plans

[12] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers*; see also the guidance for industry *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs.*

no later than 60 days after an end-of-phase 2 meeting.[13] Extrapolation of adult efficacy findings to pediatrics is generally acceptable. However, studies are typically needed to determine the appropriate dose and provide an assessment of the safety of the drug in the pediatric population. The pharmacokinetic (PK) information of the drug in specific populations (e.g., geriatric patients, patients with renal or hepatic impairment) should be evaluated to determine whether dose adjustments are necessary.

6. Dose Selection

To choose the dose or doses to be evaluated in phase 3 clinical trials, sponsors should integrate the findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics, safety and tolerability information from phase 1 clinical trials, and safety and efficacy information from phase 2 dose-ranging clinical trials. Trials assessing drug penetration at the site of action (e.g., epithelial lining fluid) may be helpful in defining doses that achieve concentrations sufficient to exert an antibacterial effect.

7. Choice of Comparators and Concomitant Antibacterial Drugs

The active comparator drug should reflect the current standard of care for the treatment of HABP/VABP. When evaluating the current standard of care, we consider the recommendations by authoritative scientific bodies (e.g., American Thoracic Society, Infectious Diseases Society of America) based on clinical evidence and other reliable information that reflects current clinical practice.

Ideally, an investigational drug would fully encompass the broad spectrum of bacterial pathogens implicated in HABP/VABP. However, investigational drugs with more limited antibacterial activity can be targeted for development for the treatment of HABP/VABP, but in this case most patients would need initial concomitant antibacterial drug therapy to treat the broad spectrum of bacterial pathogens before culture results are available. Another consideration is the different patterns of bacterial etiologies responsible for HABP/VABP at each clinical trial site. Because concomitant antibacterial drugs can confound the interpretation of treatment effect in a noninferiority trial, the protocol should specify any use of concomitant antibacterial drugs that may be permitted for the initial treatment of patients with HABP/VABP.

To the extent possible, the concomitant antibacterial drug should not have antibacterial activity similar to the spectrum of activity of the investigational drug. After culture and in vitro susceptibility testing results are available, if there is a defined level of clinical improvement, sponsors should consider de-escalation of concomitant therapy.[14] Whenever possible, treatment

[13] See the Pediatric Research Equity Act (Public Law 108-155; section 505B(e)(2)(A) of the FD&C Act; 21 U.S.C. 355B) as amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144). See also the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

[14] For example, see the recommendations for *de-escalation* of the initial empirical antibacterial drug therapy based on the culture results and in vitro susceptibility testing in the setting of clinical improvement at 48 to 72 hours (ATS 2005).

should be completed as monotherapy with the investigational drug in patients randomized to the investigational drug group, enhancing the possibility of drawing stronger conclusions about an investigational drug's overall treatment effect.

8. Prior Antibacterial Drug Therapy

Ideally, patients enrolled in an HABP/VABP clinical trial would not have received prior antibacterial drug therapy. Prior therapy can have important consequences for a clinical trial. Specifically, prior antibacterial drug therapy could obscure true treatment differences between an investigational drug and the control drug, introducing bias toward a finding of no difference between treatment groups (i.e., a bias toward a finding of noninferiority; see, for example, Pertel, Bernardo, et al. 2008). However, a complete ban on all patients who have received prior antibacterial therapy also could have adverse consequences. Specifically, certain trial sites may decline to participate in the clinical trial because of concerns that trial treatment would not represent standard of care and would place patients at risk.

A pragmatic approach to these concerns is to: (1) encourage prompt enrollment procedures (e.g., anticipatory informed consent offered to any patient on the first day of hospitalization) so that patients can receive the clinical trial treatment initially, with no need for other antibacterial drug therapy; and (2) allow enrollment of patients who have received not more than 24 hours of therapy before enrollment. This would permit patients in the trial to receive prompt antibacterial drug therapy that is determined to be clinically necessary.

9. Efficacy Endpoints

Before the introduction of antibacterial drug therapy, mortality rates among untreated patients who had pneumonia and comorbid conditions (e.g., patients older than 60 years of age) exceeded 50 percent (Finland, Spring, et al. 1940). In patients with HABP/VABP, we found that mortality rates among patients who did not receive effective antibacterial drug treatment also exceeded 50 percent (see the Appendix; the lower bound of the two-sided 95 percent confidence interval of the all-cause mortality rate was 52 percent). Thus, in the absence of effective antibacterial drug therapy, only approximately 50 percent of patients who have HABP/VABP are expected to survive. Based on the results of recently conducted trials, approximately 80 percent or more of patients who receive effective antibacterial drug therapy for HABP/VABP will survive.[15] The antibacterial drug treatment effect on survival is large enough to support an efficacy finding based on the noninferiority of an investigational drug to a control drug based on a survival endpoint (see the Appendix).

[15] See the Appendix, as well as the November 4, 2011, Anti-Infective Drugs Advisory Committee meeting transcripts and slides that can be found at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm242307.htm.

a. Primary endpoints

Sponsors should select one of the following two primary efficacy endpoints for clinical trials:

- A primary endpoint based on survival: all-cause mortality can be evaluated at a fixed time point at any time between day 14 and day 28 (see the Appendix).

- A primary endpoint based on survival and no disease-related complications: all-cause mortality or disease-related complications (e.g., development of empyema; onset of acute respiratory distress syndrome; other complications) can be evaluated at a fixed time point at any time between day 14 and day 28. Sponsors should discuss with the FDA the disease-related complications in advance of trial initiation.

In general, the primary efficacy analysis should be based on a comparison of the proportions of patients achieving the primary endpoint at a fixed time point.

b. Secondary endpoints

Secondary endpoints can include the following: (1) an assessment of resolution of signs and symptoms of HABP/VABP at approximately 7 to 14 days after the completion of antibacterial drug treatment; (2) days spent in the hospital; and (3) days spent on mechanical ventilation (for VABP and ventilated-HABP patients).

10. Trial Procedures and Timing of Assessments

a. Entry visit

At the entry visit, sponsors should collect baseline demographics, clinical information, sputum specimen for evaluation and culture, and baseline laboratory tests, as appropriate.

b. On-therapy and end-of-therapy visits

Patients should be evaluated during therapy and at the end of prescribed therapy. Clinical and laboratory assessments for safety should be performed as appropriate.

c. Visits after completion of therapy

At approximately 7 to 14 days following completion of antibacterial therapy, patients should be evaluated for continued clinical response or resolution of HABP/VABP, as well as safety evaluations. Mortality should be assessed, including a mortality assessment at day 28.

11. Statistical Considerations

In general, sponsors should provide a detailed statistical analysis plan stating the trial hypotheses and the analysis methods before trial initiation. The primary efficacy analysis should be based

on the difference between treatment groups in the proportions of success on the primary outcome measure, assessing either noninferiority or superiority.

a. Analysis populations

The following definitions apply to various analysis populations:

- Intent-to-treat (ITT) population — All randomized patients.

- Safety population — All patients who received at least one dose of drug during the trial.

- Microbiological intent-to-treat (micro-ITT) population — All randomized patients who have a baseline bacterial pathogen identified as the cause of HABP/VABP against which the investigational drug has antibacterial activity. This includes bacterial pathogens identified by standard culture methods in a respiratory specimen or blood specimen. In addition, nonculture methods of detection of bacterial pathogens (e.g., urinary antigen test) can be used to identify patients for inclusion in a micro-ITT analysis population.

- Per-protocol populations — Patients who follow important components of the trial as specified in the protocol.

- Per-protocol microbiologically evaluable populations — Patients who follow important components of the trial as specified in the protocol and have a baseline bacterial pathogen identified as the cause of HABP/VABP.

The appropriate primary efficacy analysis population depends on the enrollment criteria for the trial and the spectrum of activity of the investigational drug. For example, if an investigational drug has activity against gram-positive bacterial pathogens, the micro-ITT population (patients who have a baseline gram-positive bacterial pathogen identified as the cause of HABP/VABP by standard culture methods or nonculture methods of detection) can represent the primary efficacy analysis population. An alternative approach is the requirement of an additional entry criterion based on the findings from the Gram stain (e.g., gram-positive bacteria on high-power view of the respiratory specimen before randomization). In this alternative approach, the ITT population of all randomized patients would represent the primary efficacy analysis population, with the micro-ITT population to be evaluated in an important secondary efficacy analysis. Other populations should be evaluated for consistency of the results that were observed in the primary efficacy analysis population.

b. Noninferiority margins

The historical data support the appropriateness of noninferiority trials for the HABP/VABP indication (see the Appendix). For example, using a survival endpoint, a noninferiority margin of 10 percent can be supported by the historical evidence, which supports a reduction in mortality by effective therapy of about 20 percent. A 10 percent noninferiority margin supports a preservation of a meaningful fraction of that effect. Sponsors should discuss with the FDA the selection of a noninferiority margin greater than 10 percent.

c. Sample size considerations

In one example of a sample size calculation, approximately 268 patients per group is estimated for the ITT analysis population based on the rate of all-cause mortality of 15 percent in the control group and a noninferiority margin of 10 percent. The trial will rule out a greater than 10 percent inferiority of the investigational drug to control drug (an upper bound of the two-sided 95 percent confidence interval for the difference in the rates of all-cause mortality of the control drug minus the investigational drug).

C. Other Considerations

1. Relevant Nonclinical Development Considerations

Animal models of acute pneumonia have been developed and may contribute to evaluating antibacterial activity. Animal studies are not a substitute for the clinical trials in patients with HABP/VABP that must be conducted to evaluate safety and efficacy of the drug.[16]

2. Pharmacokinetic/Pharmacodynamic Considerations

Sponsors should evaluate the PK/pharmacodynamic (PD) characteristics of the drug using in vitro models and animal models of infection. The results from nonclinical PK/PD assessments should be integrated with the findings from phase 1 PK assessments to help identify appropriate doses and dosing regimens for evaluation in phase 2 and phase 3 clinical trials. Plasma drug concentrations should be determined from patients in phase 2 clinical trials. Using the plasma concentration data, the sponsor should assess the relationship between antibacterial PK/PD indices[17] and observed clinical and microbiological outcomes. Antibacterial PK/PD indices relate a measure of drug exposure to the minimum inhibitory concentration value. The evaluation of exposure-response relationships (efficacy and safety) in phase 2 can help determine the best dose for evaluation in phase 3 trials.

Sponsors should determine plasma drug concentrations from patients in phase 3 clinical trials. If phase 3 trials include a previously unstudied specific population, such as patients with renal or hepatic impairment, collection of plasma drug concentrations from those specific populations can aid in determining necessary dose adjustments. PK data from patients studied in phase 3 also can help interpret any unexpected safety or efficacy findings via evaluation of exposure-response relationships.

[16] See 21 CFR 314.600.

[17] Antibacterial PK/PD indices include maximal unbound drug concentration [fC_{max}]/ minimum inhibitory concentration (MIC) ratio, area under the unbound drug concentration-time curve [fAUC]/MIC ratio, or the percentage of the dosage interval that the unbound drug concentration exceeds the MIC [fT>MIC].

3. Labeling Considerations

In general, the labeled indication should reflect the patient population enrolled in the clinical trials. For example, a successful development program enrolling patients who have HABP alone and did not receive mechanical ventilation likely would support a labeled indication for the treatment of HABP. All other development programs that include approximately 50 percent of patients who have VABP generally will support a labeled indication for the treatment of HABP and VABP (see section III.B.2., Trial Population).

REFERENCES

Alvarez-Lerma, F, J Insausti-Ordenana, R Jorda-Marcos, et al., 2001, Efficacy and Tolerability of Piperacillin/Tazobactam Versus Ceftazidime in Association With Amikacin for Treatment of Nosocomial Pneumonia in Intensive Care Patients: A Prospective, Randomized, Multicenter Trial, Intensive Care Med, 27:493-502.

American Thoracic Society, 2005, Guidelines for the Management of Adults With Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated Pneumonia, Am J Respir Crit Care Med, 171:388-416.

DerSimonian, R and N Laird, 1986, Meta-Analysis in Clinical Trials, Controlled Clin Trials, 7:177-188.

Fink, MP, DR Snydman, MS Neiderman, et al., 1994, Treatment of Severe Pneumonia in Hospitalized Patients: Results of a Multicenter, Randomized, Double-Blind Trial Comparing Intravenous Ciprofloxacin With Imipenem/Cilastatin, Antimicrob Agents Chemother, 38:547-557.

Finland, M, WC Spring, and FC Lowell, 1940, Specific Treatment of the Pneumococcic Pneumonias; An Analysis of the Results of Serum Therapy and Chemotherapy at the Boston City Hospital From July 1938 Through June 1939, Annals of Internal Medicine,13(9):1567-1593.

Kollef, MH and S Ward, 1998, The Influence of Mini-BAL Cultures on Patient Outcomes: Implications for the Antibiotic Management of Ventilator-Associated Pneumonia, Chest, 113:412-420.

Luna, CM, P Aruj, MS Neiderman, et al., 2006, Appropriateness and Delay to Initiate Therapy in Ventilator-Associated Pneumonia, Eur Respir J, 27:158-164.

Pertel, PE, P Bernardo, C Fogarty et al., 2008, Effects of Prior Effective Therapy on the Efficacy of Daptomycin and Ceftriaxone for the Treatment of Community-Acquired Pneumonia, Clin Infect Dis, 46:1142-1151.

Rubinstein, E, SK Cammarata, TH Oliphant, et al., 2001, Linezolid (PNU-100766) Versus Vancomycin in the Treatment of Hospitalized Patients With Nosocomial Pneumonia: A Randomized, Double-Blind, Multicenter Study, Clin Infect Dis, 32:402-412.

Sorbello, A, S Komo, T Valappil, S Nambiar, 2010, Registration Trials of Antibacterial Drugs for the Treatment of Nosocomial Pneumonia, Clin Infect Dis, 51(S1):S36-S41.

West, M, BR Boulanger, C Fogarty, et al., 2003, Levofloxacin Compared With Imipenem/Cilastatin Followed By Ciprofloxacin in Adult Patients With Nosocomial Pneumonia: A Multicenter, Prospective, Randomized, Open-Label Study, Clin Ther, 25:485-506.

494 Wunderink, RG, SK Cammarata, TH Oliphant, et al., 2003, Continuation of a Randomized,
495 Double-Blind, Multicenter Study of Linezolid Versus Vancomycin in the Treatment of Patients
496 With Nosocomial Pneumonia, Clin Ther, 25:980-992.
497

APPENDIX:
SUPPORT FOR A NONINFERIORITY MARGIN FOR CLINICAL TRIALS EVALUATING ANTIBACTERIAL DRUGS FOR TREATMENT OF HABP/VABP

The usual source of information about the effect of the control drug, the basis for specifying a noninferiority margin, is placebo-controlled trials. Such trials do not exist for HABP/VABP. This Appendix describes an approach to providing historical evidence of sensitivity to drug effect and support for the noninferiority margin by comparing trials using inadequate or delayed treatment and trials using effective antibacterial drug treatment.

A literature search identified a total of seven trials that evaluated patients who had HABP/VABP. Two trials evaluated patients who received inadequate or delayed treatment and five trials were prospective, controlled trials of effective antibacterial drug treatment. Patients in the seven trials had similar baseline demographic characteristics. Clinical responses were not provided in a standardized or consistent manner in any of these trials, so that only all-cause mortality was identified in these trials as a well-defined and reliable clinical endpoint. The all-cause mortality reporting time period for these evaluations was variable (e.g., 30 days after completion of therapy; 28 days after onset of HABP/VABP; 12 days after completion of therapy) or was not reported at all. Tables 1 and 2 provide the results of all-cause mortality observed in each arm of the trials.

Table 1. Nonrandomized Evaluations Involving Inadequate or Delayed Treatment in Hospitalized Patients With HABP/VABP

Trial	Number of Patients (% Ventilator-Associated)	**Inadequate or Delayed Treatment All-Cause Mortality n/N (%)**	Appropriate Treatment All-Cause Mortality n/N (%)
Kollef and Ward 1998	102* (100%)	**31/51 (61%)**	17/51 (33%)
Luna, Aruj, et al. 2006	76 (100%)	**33/52 (64%)**	7/24 (29%)

*The trial evaluated 130 patients who were receiving mechanical ventilation, and 28 patients did not have evidence to support a diagnosis of VABP.

A random effects meta-analysis (DerSimonian and Laird 1986) for the estimate of mortality in patients who received inadequate or delayed treatment was 62 percent (95 percent confidence interval 52 percent, 71 percent). An all-cause mortality rate was lower in patients who received appropriate treatment in these nonrandomized trials.

Table 2. Prospective, Controlled Clinical Trials Using Effective Antibacterial Drug Treatment in Patients With HABP/VABP

Trial	Number of Patients (% Ventilator-Associated)	**Effective Treatment Group 1* All-Cause Mortality n/N (%)**	**Effective Treatment Group 2* All-Cause Mortality n/N (%)**
Alvarez-Lerma, Insausti-Ordenana, et al. 2001	124 (85.5%)	**P/T/A 27/88 (31%)**	**Cef/A 8/36 (22%)**
Fink, Snydman, et al. 1994	402 (75.6%)	**Imi 38/200 (19%)**	**Cip 43/202 (21%)**
Rubinstein, Cammarata, et al. 2001	396 (57.3%)	**Lin/Az 36/203 (18%)**	**Van/Az 49/193 (25%)**
West, Boulanger, et al. 2003	438 (10.7%)	**Imi/Cip 32/218 (15%)**	**Lev/Lev PO 38/220 (17%)**
Wunderink, Cammarata, et al. 2003	623 (50.6%)	**Lin/Az 64/321 (20%)**	**Van/Az 61/302 (20%)**

* The data in the table are presented by the treatment groups (1 and 2) for these active-controlled trials; A = amikacin; Cef = ceftazidime; Cip = ciprofloxacin; Imi = imipenam/cilastatin; Lev = levofloxacin; P/T = piperacillin/tazobactam; Lin = linezolid; Az = Aztreonam; Van = vancomycin.

The estimate of mortality based on a random effects meta-analysis (DerSimonian and Laird 1986) in patients who received effective antibacterial drug treatment (all 10 treatment groups from the 5 trials) was 20 percent (95 percent confidence interval 18 percent, 23 percent). The meta-analyses yielded a lower bound estimate of all-cause mortality for inadequate or delayed treatment of HABP/VABP of 52 percent and an upper bound estimate of all-cause mortality among effective antibacterial drug treatment of 23 percent. An estimate of the treatment effect of an antibacterial drug over inadequate or delayed treatment is approximately 29 percent (52 percent *minus* 23 percent). Allowing for some uncertainty of the results from these nonrandomized comparisons, we consider an acceptable effectiveness margin of the active control drug relative to placebo (M_1) to be 20 percent. Therefore, we consider a noninferiority margin (M_2) of 10 percent to be reasonable both clinically and statistically. Sponsors can discuss with the FDA the selection of a noninferiority margin that is greater than 10 percent.