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

Guidance for Industry

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

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Clinical/Antimicrobial

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

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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 FDA's current thinking about the overall development program and clinical trial designs for drugs to support an indication for treatment of HABP/VABP.

This guidance does not discuss the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* (September 1998) and *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001), respectively.[3]

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

II. BACKGROUND

[1] This guidance has been prepared by the Division of Anti-Infectives in the Center for Drug Evaluation and Research 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] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

HABP/VABP occurs in hospitalized patients and in patients who have been recently discharged from the hospital. A hospital stay of 48 hours or more places patients at risk for infection with a variety of organisms, including gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* and gram-negative bacteria such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* species.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Nonclinical Development Considerations

In addition to the expected nonclinical pharmacology/toxicology studies (see Section III. C. 1, Pharmacokinetic/Pharmacodynamic Considerations), sponsors should provide nonclinical data from in vitro studies and in vivo animal studies[4] demonstrating activity against one or more of the commonly implicated pathogens for HABP/VABP.[5]

2. Drug Development Population

HABP is 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.[6] Patients with HABP may or may not require intubation and mechanical ventilation.

VABP is 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. These signs and symptoms are in addition to laboratory abnormalities such as leukocytosis accompanied by the presence of a new or progressive infiltrate on a chest radiograph in a patient on mechanical ventilation for a minimum of 48 hours.

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

[5] See the guidelines from the American Thoracic Society and the Infectious Diseases Society of America (Kalil et al. 2016), or other relevant publications, for descriptions of bacterial pathogens commonly identified in patients with HABP/VABP.

[6] Oral and nasotracheal bacterial flora may not return to normal flora within 4 to 6 weeks or longer after hospitalization.

3. Efficacy Considerations

A showing of superiority or noninferiority, using an acceptable noninferiority margin, to a control drug in the treatment of HABP/VABP is readily interpretable as evidence of effectiveness (see the Appendix).[7]

The Agency generally expects sponsors to conduct two adequate and well-controlled trials in HABP/VABP to establish substantial evidence of effectiveness. Alternatively, a single adequate and well-controlled trial in HABP/VABP with confirmatory evidence (e.g., the results of a trial in another infectious disease indication) can provide substantial evidence of effectiveness.[8] Sponsors should discuss with the FDA the confirmatory evidence that would be used to support the efficacy findings from a single trial in HABP/VABP.

4. Safety Considerations

If the same or greater dose and treatment duration for HABP/VABP were used in clinical trials for other infectious disease indications, safety data from these indications can be used to support safety for HABP/VABP. Sponsors should discuss with the FDA the appropriate size of the premarketing safety database during clinical development.

5. Clinical Microbiology Considerations

An adequate sputum specimen should be processed by a laboratory according to recognized methods for Gram stain, culture, and in vitro antibacterial susceptibility testing.[9]

Use of rapid diagnostic or nonculture tests may help identify a patient for enrollment in an HABP/VABP trial. If the tests being used are not FDA cleared, sponsors should provide sufficient information about the performance characteristics of the tests determined from analytical validation studies.

The clinical trial of an antibacterial drug also may provide an opportunity to develop and evaluate a new diagnostic test. Sponsors interested in using a clinical trial in patients with HABP/VABP as a means to also evaluate a diagnostic test are encouraged to discuss this with the Agency.

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

[8] See the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[9] 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.

B. Specific Efficacy Trial Considerations

1. Trial Design

HABP/VABP trials should be randomized and double-blind when possible, comparing the investigational drug with an active control. In general, HABP/VABP trials will be designed as noninferiority trials. Another trial design is the add-on superiority design, in which patients receive either a placebo or an investigational drug added to standard-of-care antibacterial drug therapy.

2. Trial Population

For an indication for the treatment of HABP/VABP, the trial population should consist of patients who have HABP (regardless of mechanical ventilation) or VABP. The trial population should include at a minimum approximately 50 percent of patients who are on mechanical ventilation at enrollment (VABP/ventilated HABP). Sponsors interested in seeking an indication for HABP only should discuss the trial design and trial population with the Agency.

The protocol can specify the use of a clinical severity scoring system to identify a trial population consisting of patients who have a sufficient severity of illness to maintain assay sensitivity for the all-cause mortality endpoint in a noninferiority trial (e.g., at least a 15 percent mortality rate). An example of a clinical severity scoring system is the Acute Physiology and Chronic Health Evaluation II.

3. Inclusion and Exclusion Criteria

a. Inclusion criteria

Patients should have at least one of the following clinical features:

- New onset or acute 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
- Need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation or needed changes in the amount of positive end-expiratory pressure
- New onset of suctioned respiratory secretions

In addition, patients should have at least one of the following signs/laboratory abnormalities:

- Documented fever (e.g., body temperature greater than or equal to 38°C)

- Hypothermia (e.g., core body temperature less than or equal to 35°C)
- Total peripheral white blood cell count greater than or equal to 10,000 cells per cubic millimeter (mm^3)
- Leukopenia with total white blood cell count fewer than or equal to 4,500 cells per mm^3
- Greater than 15 percent immature neutrophils (e.g., bands) noted on peripheral blood smear

Plus

- A chest radiograph showing the presence of a new or progressive infiltrate suggestive of bacterial pneumonia

b. 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

The protocol should specify randomization of patients 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) could be considered in certain situations (e.g., to enhance the size of the safety database of the investigational drug). To the extent possible, the trial should be double-blinded. If there is a compelling reason for single-blind or open-label trial designs, sponsors should discuss with the Agency efforts to minimize bias before initiating the trial.

Sponsors should consider methods to enhance the efficiency of the enrollment and randomization processes and enable prompt administration of antibacterial drug therapy within the context of the clinical trial, thus avoiding the potential confounding by effective antibacterial drug therapy before enrollment (see section III. B. 8., Prior Antibacterial Drug Therapy). For example, it often may be the case that few HABP/VABP patients are enrolled at each clinical center. In this case, sponsors may consider randomizing centers rather than individual patients to simplify enrollment, with appropriate adjustments to the statistical analysis plan and informed consent procedures to accommodate cluster randomization. As another example, sponsors could give hospitalized patients at risk for developing HABP/VABP informed consent in anticipation of participating in a clinical trial if the patient develops HABP/VABP (Corneli et al. 2018).

5. Specific Populations

The trials should include patients of both sexes, patients of all races, and geriatric patients.[10] The FDA encourages sponsors 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 no later than 60 days after an end-of-phase 2 meeting.[11] Extrapolation of adult efficacy findings in HABP/VABP to pediatrics is generally acceptable. However, studies are typically needed to determine the appropriate dose and assess the safety of the drug in the pediatric population. Sponsors should evaluate the pharmacokinetic (PK) information of the drug in specific populations (e.g., geriatric patients, patients with renal or hepatic impairment) 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.

For products with both intravenous and oral formulations, sponsors should collect PK data in earlier phase studies to select the appropriate oral dose for the intravenous-to-oral switch.

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, the FDA considers 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 have activity against most bacterial pathogens implicated in HABP/VABP and concomitant antibacterial drugs would not be necessary. However,

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[10] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* (August 1994) and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers* (February 2012); see also the guidance for industry *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs* (July 1993).

[11] 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* (March 2016). When final, this guidance will represent the FDA's current thinking on this topic.

investigational drugs with a narrow spectrum of antibacterial activity can be developed for the treatment of HABP/VABP. 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 treating patients with HABP/VABP and address the impact these concomitant drugs may have on study conclusions.

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-escalating concomitant therapy.[12] Whenever possible, treatment should be completed as monotherapy with the investigational drug in patients randomized to the investigational drug group.

8. Prior Antibacterial Drug Therapy

Ideally, patients enrolled in an HABP/VABP clinical trial would not have received prior antibacterial drug therapy. Prior antibacterial drug 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 et al. 2008). However, excluding patients who have received prior antibacterial drug 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 patients at risk for developing HABP/VABP) 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 no more than 24 hours of therapy before enrollment. Patients who have objective documentation of clinical failure while receiving any duration of prior antibacterial drug therapy for treatment of HABP/VABP can be enrolled.

9. Efficacy Endpoints

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).

[12] 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 (American Thoracic Society 2005).

- 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, sepsis 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 Agency the disease-related complications before initiating the trial.

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 from randomization.

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 therapy, (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, the protocol should specify the collection of baseline demographics, clinical information, sputum specimen for evaluation and culture, and baseline laboratory tests, as appropriate.

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

The protocol should specify an evaluation of patients during therapy and at the end of therapy and should specify clinical and laboratory assessments for safety as appropriate.

c. Visits after completion of therapy

The protocol should specify evaluations for continued clinical response or resolution of HABP/VABP and safety at approximately 7 to 14 days after patients complete antibacterial therapy. Sponsors should assess and report mortality, including a mortality assessment at day 28.

11. Statistical Considerations

In general, sponsors should provide, before trial initiation, 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 known to cause HABP/VABP that is susceptible to the investigational drug and active control, identified from an appropriate sputum or blood specimen.
- Per-protocol populations — Patients who are not lost to follow-up and adhere to trial procedures as specified in the protocol.
- Per-protocol microbiologically evaluable populations — Patients who are characterized in the per-protocol population and have a baseline bacterial pathogen identified as the cause of HABP/VABP.

Sponsors should discuss with the Agency the prespecified primary analysis population before initiating the trial. In general, it is acceptable to consider the ITT population as the primary analysis population. For antibacterial drugs with a narrow spectrum of activity (e.g., a drug active against a single genus and species of bacteria), the micro-ITT population will be considered the primary analysis population.

b. Noninferiority margins

Historical data support the appropriateness of noninferiority trials for HABP/VABP (see the Appendix). For example, with the use of 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. If a noninferiority margin >10 percent is selected, sponsors should discuss the rationale and justification with the Agency.

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 test and control groups and a noninferiority margin of 10 percent. The trial will rule out greater than 10 percent inferiority of the investigational drug to the 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. Pharmacokinetic/Pharmacodynamic Considerations

Sponsors should evaluate the PK/pharmacodynamic (PD) characteristics of the drug using in vitro methods and animal models of infection. Sponsors should also consider the limitations of such models before evaluating the antibacterial drug (Tessier et al. 2002; Gavaldà et al. 1997; Legget 1999; Miyazaki et al. 1997; Silverman et al. 2005).

Integration of these PK/PD characteristics of the drug with the findings from phase 1 clinical trials can assist identification of appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical trials.[13]

Sponsors should obtain blood samples from patients in phase 2 and phase 3 clinical trials (sparse sampling) to estimate drug exposure in each patient. Sponsors should perform an exposure-response analysis for clinical outcomes, microbiologic outcomes, and clinically relevant adverse events. If phase 3 trials include a previously unstudied specific population, such as patients with renal or hepatic impairment, collecting plasma drug concentrations from those specific populations can aid in determining necessary dose adjustments.

2. Labeling Considerations

Generally, the labeled indication should reflect the patient population (HABP, VABP, or HABP/VABP) enrolled in the clinical trials.

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

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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 hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (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 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 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 et al. 2006	76 (100%)	33/52 (64%)	7/24 (29%)

*The trial evaluated 130 patients who were receiving mechanical ventilation, 28 of whom 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 to 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 Therapy 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 et al. 2001	124 (85.5%)	P/T/A 27/88 (31%)	Cef/A 8/36 (22%)
Fink et al. 1994	402 (75.6%)	Imi 38/200 (19%)	Cip 43/202 (21%)
Rubinstein et al. 2001	396 (57.3%)	Lin/Az 36/203 (18%)	Van/Az 49/193 (25%)
West et al. 2003	438 (10.7%)	Imi/Cip 32/218 (15%)	Lev/Lev PO 38/220 (17%)
Wunderink 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 to 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, the Agency considers an acceptable effectiveness margin of the active-control drug relative to placebo (M_1) to be 20 percent. Therefore, the Agency considers a noninferiority margin (M_2) of 10 percent to be reasonable both clinically and statistically. Sponsors can discuss with the Agency the selection of a noninferiority margin that is greater than 10 percent.