DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Division of Anti-Infective Products/Office of Antimicrobial Products

Briefing Document

Endpoints and Clinical Trial Issues in Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

Anti-Infective Drugs Advisory Committee

November 4, 2011

Table of Contents

I. Introduction

A public workshop, cosponsored by the U.S. Food and Drug Administration (FDA), the Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS), the Society of Critical Care Medicine (SCCM), and the American College of Chest Physicians (ACCP), was held on March 31 and April 1, 2009 and included participants from FDA, academia, and industry. The participants at this workshop discussed scientific issues in clinical trial design for hospital-acquired and ventilator-associated pneumonia, including diagnosis, effect of antimicrobial treatment, endpoints, and statistical issues in trials in hospital-acquired and ventilator-associated pneumonia.[1]

Based in part, on the discussions at the workshop, a draft guidance entitled, "Guidance for Industry: Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia, Developing Drugs for Treatment" was issued in November 2010. Justification for a noninferiority margin for clinical trials in Hospital-Acquired Bacterial Pneumonia (HABP)/Ventilator-Associated Bacterial Pneumonia (VABP) was provided in an appendix. We received a number of comments to the docket on the draft guidance that criticized several aspects of the guidance. In general, most of the comments expressed concerns that the guidance outlined a clinical development program for HABP and VABP that was not feasible to conduct.

The purpose of the Anti-Infective Drugs Advisory Committee (AIDAC) meeting on November 4, 2011 is to discuss some of the issues pertaining to clinical trials for HABP/VABP in order to get advice on scientifically sound, ethical and feasible approaches to studying drugs for HABP/VABP. It is important to have ongoing antibacterial drug development to address current and future public health needs for treatments for patients with HABP/VABP. It is also essential that current and future antibacterial drugs be used prudently.

The questions posed at this meeting of the AIDAC will focus the discussions on several issues regarding clinical trials for HABP/VABP. We seek the advice of the AIDAC on the following specific areas for HABP/VABP clinical trials:

1. Primary efficacy endpoint of all-cause mortality, expected rates of mortality, and timing of assessment of mortality
2. Number of Phase 3 trials and the use of supportive evidence
3. Use of prior and concomitant antibacterial drugs
4. Microbiological Intent to Treat as the primary analysis population
5. Appropriate noninferiority margins and approaches to analyses (e.g. metrics to use for analyses such as risk difference vs. odds ratio)

[1] Presentations and transcripts from the workshop are available at: http://www.fda.gov/Drugs/NewsEvents/ucm169877.htm.

Discussions at the workshop were also summarized in a supplement to *Clinical Infectious Diseases* Volume 51 Supplement 1 August 1, 2010 available at http://cid.oxfordjournals.org/content/51/Supplement_1.toc

II. Discussion Topics for Clinical Development Programs for HABP/VABP

A. All-cause Mortality Endpoint

Several comments submitted to the docket noted that mortality may not be an appropriate endpoint and that clinical response is a more meaningful endpoint that reflects the treatment effect of antibacterial drugs. Based on these comments received in the docket, we reviewed the historical data again in an attempt to identify a possible clinical endpoint other than all-cause mortality. Our review of the historical data did not find evidence that would allow an estimate of a treatment effect based on a non-mortality clinical response endpoint. As noted in the section on noninferiority margin justification in the draft guidance, the only endpoint for which we have been able to determine an antibacterial treatment effect based on information reviewed to date is all-cause mortality.

B. Number of Trials and Role of Supportive Information

Some of the docket comments provided criticism regarding the practicability of conducting a clinical development program for an antibacterial drug for HABP/VABP based in part, on estimates of sample sizes needed for two trials as described in the 2010 draft guidance. Considering these comments and the potential role of supporting information for an antibacterial drug, this background document describes for purposes of discussion a clinical development program for HABP/VABP based on a single adequate and well-controlled trial using an all-cause mortality endpoint with additional supportive information. [2] Other supportive information should accompany the single Phase 3 trial such as evidence of efficacy and safety in other clinical conditions, Phase 2 trial(s), and data from efficacy in animal models of infections and *in vitro* studies.

C. Use of Prior and Concomitant Antibacterial Drugs

The draft HABP/VABP guidance recommends exclusion of patients who had received prior antibacterial drugs that have activity against bacterial pathogens that cause HABP/VABP within the preceding 30 days, because of the potential to bias the results of a trial towards a finding of noninferiority. There are two issues pertinent to prior use of antibacterial drugs in clinical trials of HABP/VABP. As patients developing HABP/VABP are usually hospitalized for a period of time before developing pneumonia, there is a high likelihood that these patients, especially those with VABP, would have received antibacterial drugs for treatment of other infections. As with other indications, patients who have an organism identified on culture at study entry that is resistant to their current therapy or not within the spectrum of the current therapy are eligible for enrollment in the trial. A similar approach may need to be considered for HABP/VABP trials. The second issue is receipt of antibacterial drugs for HABP/VABP prior to enrollment in the trial. In community acquired pneumonia, prior antibacterial drug

[2] FDA guidance: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3621b1_20_tab16.pdf

therapy impacts clinical outcomes. [3] In HABP/VABP, we are not aware of information that allows an assessment of the impact of prior antibacterial drug therapy (e.g. whether a single-dose of antibacterial drug(s) or even a short course of antibacterial therapy (≤ 24 hours) will have an impact on the outcome of 28-day mortality). The issue is whether prior antibacterial drug therapy will cloud the assessment of the effect of the investigational drug; this is a particularly important concern with noninferiority trials.

Concomitant antibacterial drugs pose a special problem in patients with HABP/VABP as the standard of care is to provide broad-spectrum coverage until de-escalation of therapy is possible. In addition, for investigational agents with limited spectrum of activity such as activity against only Gram-positive bacteria, there is need for additional antibacterial drugs to ensure coverage of the likely pathogens. However, many of these antibacterial drugs also have overlapping activity against Gram-positive bacteria, making it difficult to interpret the trial results. Thus it is very important that careful attention be paid to the antibacterial spectrum of the concomitant antibacterial drugs being used in the trials and to minimize the use of antibacterials with overlapping activity, to the extent possible. The protocols should specify the permissible concomitant therapies.

We plan to review data available from previously conducted HABP/VABP trials in an attempt to identify data that can be analyzed to address the question of the impact of prior antibacterial drug therapy on patient outcomes such as mortality. One additional consideration for possible future studies may be to model the impact of prior antibacterial therapies using appropriate animal models of infection.

D. Microbiological Intent to Treat as the Primary Analysis Population

The draft guidance recommends that the microbiological Intent-to-Treat (micro-ITT) be the primary analysis population. The micro-ITT is preferred over the ITT population because of clinical and radiological diagnostic uncertainties with HABP /VABP. The micro-ITT population gives greater confidence that patients enrolled in the trials have HABP/VABP. In addition, unlike in community acquired bacterial pneumonia, it is possible to make a microbiological diagnosis in a higher proportion of patients, especially in VABP patients. Based upon our review of more recent trials we found that approximately 70% of VABP patients had a microbiological etiology identified on routine culture. Finally, as such patients often receive antibacterial drugs with overlapping spectrum of activities or if the test drug has a limited antibacterial spectrum of activity, it is important to have a microbiologic diagnosis in order to adequately assess the effect of an investigational drug in a HABP/VABP clinical trial.

Conventional sputum culture is needed for the evaluation of microbiological data including the characterization of *in vitro* susceptibility testing. Non-culture methods for microbiologic diagnosis may be an option to increase the microbiologic evaluability rates beyond what can be attained with conventional culture techniques alone, which in turn impacts on sample size calculations. Non-culture tests can be used to supplement the

[3] Pertel PE, Bernardo P, Fogarty C et al. effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. Clin Infect Dis 2008;46:1142-51

microbiologic diagnosis made by conventional sputum cultures in patients with a high suspicion for VABP/HABP. A test that is approved/cleared by FDA represents a straightforward approach to consider. Tests that have not been approved/cleared by FDA may still be used for the purpose of defining the micro-ITT analysis population, if appropriate data on the performance characteristics are submitted to the FDA for review. Based on our review, it would be determined whether or not the test is an acceptable means to identify patients for inclusion in the micro-ITT analysis population. If a test is used in a trial for clinical management decisions in patients (i.e., not just for identifying patients for an analysis population), an Investigational Device Exemption (IDE) may be necessary and advice from FDA should be sought before the trial is initiated.

E. Approach to the Noninferiority (NI) Margin and Analyses

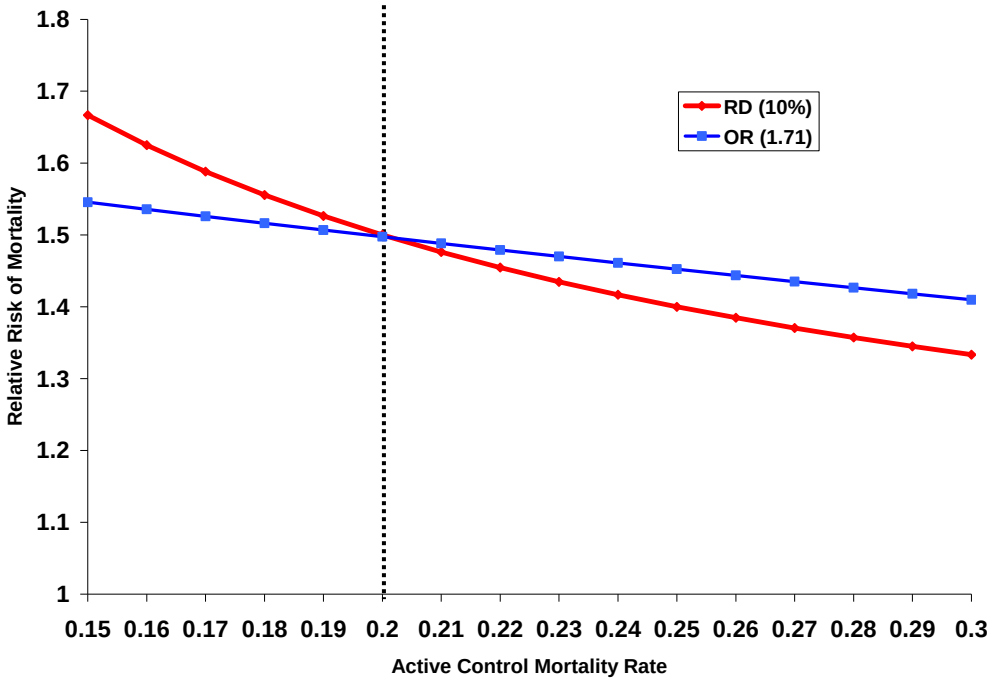
The historical evidence of antibacterial treatment effect in patients with HABP/VABP was estimated based on trials where the control mortality rate was approximately 20%. If the observed control mortality rates fall markedly below 20%, there may be concerns about the constancy assumption for the control effect and the applicability of the historical evidence of treatment effect to the actual patient population enrolled in the trial, irrespective of the effect metric used. It is important to consider the reasons why it is appropriate to assume that the treatment effect estimated from the historical data are applicable to the present day trial as conducted.

Risk Difference and Odds Ratio Metrics

Either risk difference (RD) or odds ratio (OR) can be used as the effect metric with both approaches having certain advantages and disadvantages. As mortality is an irreversible outcome, the NI margin chosen should be reasonably conservative.

Figure 1 illustrates the impact on relative risk of mortality using the RD metric (NI margin 10%) and the OR metric (NI margin 1.71). A NI margin of 1.71 for the OR metric is comparable to a 10% NI margin for the RD metric if a 20% control mortality rate is assumed. At a 20% control mortality rate, the relative risk of mortality is 1.5 using either metric. As shown in Figure 1, as the control mortality rate decreases below 20%, the relative risk of mortality is higher with the RD metric than with the OR metric.

Figure 1: Relative risk of mortality based on RD (NI margin 10%) and OR (NI margin 1.71) metrics



If the RD metric is used, assuming a 20% control mortality rate and a NI margin of 10%, the corresponding relative risk is 1.5. However, if the control mortality rate decreases, for example to 15%, the relative risk of mortality increases to 1.67 (See Table 1). This increase in the relative risk of mortality may not be clinically acceptable for a new therapy.

If the OR metric is used, assuming a 20% control mortality rate and a NI margin of 1.71, the corresponding relative risk is 1.5. However, if the control mortality rate decreases, for example to 15%, the relative risk of mortality increases to 1.55 rather than 1.67 seen with the RD metric (See Table 1).

Table 1: Relative risk of mortality corresponding to RD (NI margin 10%) and OR (NI margin 1.71) metrics

Control Mortality Rate	Relative Risk	
	RD (10%)	OR (1.71)
0.15	1.67	1.55
0.16	1.63	1.54
0.17	1.59	1.53
0.18	1.56	1.52
0.19	1.53	1.51
0.2	1.50	1.50
0.21	1.48	1.49
0.22	1.45	1.48
0.23	1.43	1.47
0.24	1.42	1.46
0.25	1.40	1.45
0.3	1.30	1.41

Sample Size Calculations:

Sample sizes calculated using the RD metric (NI margin 10%, microbiologic evaluability rate 70%, and 1:1 randomization) are shown in Table 2. Microbiologic evaluability rates may be higher if non-culture methods are used for diagnosis in addition to routine cultures. If the control mortality rate is 20%, 360 subjects will be needed per arm for a trial designed at 80% power, while 481 subjects will be needed per arm if the trial has 90% power. As the control mortality rate increases, the estimated sample size increases as shown in Table 2.

Table 2: Sample Size Calculations for the RD Metric using a 10% NI Margin:

Control Mortality Rate	Power 80% Total Subjects per Arm	Power 90% Total Subjects per Arm
15%	287	383
16%	301	404
17%	317	424
18%	331	444
19%	346	463
20%	**360**	**481**
25%	421	564
30%	471	631

Sample size calculations using the OR metric (NI margin 1.71, microbiologic evaluability rate 70%, and 1:1 randomization) are shown in Table 3. Microbiologic evaluability rates

may be higher if non-culture methods are used for diagnosis in addition to routine cultures.

One advantage of the OR metric over the RD metric is that the sample size decreases as subjects with higher mortality rates are enrolled unlike the RD metric where the sample size increases. However, if the control mortality rate is ≤20%, larger sample size will be needed if the OR metric is used.

If the control mortality rate is 20%, 476 subjects will be needed per arm for a trial designed at 80% power, while 636 subjects will be needed per arm if the trial has 90% power. As the control mortality rate increases, the estimated sample size decreases as shown in Table 3.

Table 3: Sample Size for the Odds Ratio using a NI margin of 1.71

Control Mortality Rate	Odds Ratio (NI margin=1.71)	
	Power 80% Total subjects per arm	Power 90% Total subjects per arm
15%	594	793
16%	564	753
17%	539	719
18%	516	687
19%	494	660
20%	**476**	**636**
25%	409	544
30%	366	487

In designing future trials, if there are concerns whether the actual mortality rate in a clinical trial is consistent with the estimated mortality rate used in the sample size calculation, a blinded examination of the overall mortality rate (without unblinding the individual treatment groups) can be conducted at the interim, as a blinded analysis does not introduce statistical bias. Alternatively, one could design the trial using a Group Sequential approach. However, details about the approach, necessary firewalls to protect the overall integrity of the trial, decision rules for sample size increase and the maximum sample size planned, independent Data Monitoring Committee (DMC) charter with the composition of the committee members with their conflicts of interests should be pre-specified in the protocol for review. Additional details are available in the draft guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm201790.pdf

F. Examples for Discussion of Phase 3 Trial Designs

Following is a proposal for future HABP/VABP trials:

1. A single, adequate and well-controlled noninferiority trial in VABP in addition to supportive information that will be adequate for an indication of both HABP and VABP.

2. A single, adequate and well-controlled noninferiority trial in HABP in addition to supportive information that will be adequate for an indication of HABP.

Information to support this single trial approach described above could include adequate evidence of efficacy and safety in indications such as

- Complicated Intra-Abdominal Infections (cIAI) if the investigational drug is primarily active against Gram-negative bacteria such as Enterobacteriaceae
- Community-acquired bacterial pneumonia (CABP) if the investigational drug has broad-spectrum activity that includes the common pathogens for CABP
- Acute bacterial skin and skin structure infections, if the investigational drug has activity only against Gram positive organisms including methicillin-resistant *Staphylococcus aureus*.

Key characteristics of this trial would include the following:

- Microbiologic ITT as the primary analysis population

- Primary endpoint of 28 day all-cause mortality

- The sample size is 360 subjects per arm on the risk difference metric using a 10% noninferiority margin and 476 subjects per arm on the odds ratio metric using a 1.71 noninferiority margin. These sample size calculations assume a 20% control mortality rate, 70% microbiologic evaluability rate (lower evaluability rate likely if only HABP studied), and 80% power.

- If the power is 90%, the sample size is 481 subjects per arm on the risk difference metric using a 10% noninferiority margin and 636 subjects per arm on the odds ratio metric using a 1.71 noninferiority margin.

3. Two adequate and well-controlled noninferiority trials in VABP that will be adequate for an indication of both HABP and VABP or one adequate and well-controlled trial in HABP and one in VABP that will be adequate for an indication

of both HABP and VABP as described on page 5 of the 2010 HABP/VABP draft guidance.

Key characteristics of these trials would include the following:

- Microbiologic ITT as the primary analysis population
- Assuming 70% microbiologic evaluability rate (lower evaluability rate likely if only HABP studied)
- Primary endpoint of 28 day all-cause mortality
- Noninferiority margin of 10% using the risk difference approach or 1.71 using the odds ratio metric in each trial

Topics for Discussion

1. Please discuss the merits and limitations of the single trial plus supportive information proposal for HABP/VABP. Please discuss the types of supportive evidence that would be considered acceptable if only a single trial is conducted.

2. Please discuss if a noninferiority margin of 10% will be acceptable if the active control mortality rate is less than 20%. Please discuss if the odds ratio or risk difference metric is preferred when the control mortality rate is less than 20%.

3. Please discuss the preferred timing for the all cause mortality endpoint. Would an assessment at an earlier time point be preferred to the 28-day assessment?

4. Please discuss the following scenarios regarding use of prior antibacterial drugs:
    a. Should a patient who develops HABP/VABP while receiving antibacterial drugs for other infections be enrolled in a HABP/VABP trial? If so, please discuss some scenarios where this will be acceptable.
    b. If empiric antibacterial treatment for HABP/VABP has begun prior to enrollment in the trial, what duration of therapy would be acceptable and unlikely to confound interpretation of the treatment effect of the study drug? Please describe your rationale. Please discuss what other information might be useful to address this question.

Appendix

1. Guidance for Industry: Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment, November 2010

2. Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998

3. Comments submitted to Docket No. FDA-2010-D-0589

4. Summary of Comments Submitted to Docket No. FDA-2010-D-0589

Guidance for Industry

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Joseph Toerner, MD, MPH at 301-796-1300.

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

November 2010
Clinical/Antimicrobial
Revision 1

Guidance for Industry

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

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

November 2010
Clinical/Antimicrobial
Revision 1

TABLE OF CONTENTS

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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), which are typically caused by methicillin-resistant *Staphylococcus aureus* (MRSA), Gram-negative Enterobacteriaceae such as *Klebsiella pneumoniae*, or Gram-negative non-Enterobacteriaceae such as *Pseudomonas aeruginosa* and *Acinetobacter* species. 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.[2] This draft guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective and Ophthalmology Drug Products and the Division of Special Pathogen and Transplant Drug Products, pharmaceutical sponsors, the academic community, and the public.[3]

This guidance revises and replaces the draft guidance for industry *Nosocomial Pneumonia — Developing Antimicrobial Drugs for Treatment* published in 1998. It also supersedes, with regard to the development of drugs to treat HABP/VABP, more general guidance issued many years ago (i.e., *Clinical Evaluation of Anti-Infective Drugs (Systemic)* and *Clinical Development*

[1] This guidance has been prepared by the Office of Antimicrobial 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 divisions to discuss specific issues that arise during the development of their drug product.

and Labeling of Anti-Infective Drug Products,[4] as well as the joint FDA/Infectious Disease Society of America's *General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products*.)[5]

For the purpose of this guidance, we assume that a majority of hospitalized patients will receive initial treatment with intravenous (IV) antibacterial drugs. However, this does not preclude the enrollment of hospitalized patients in oral drug trials of HABP/VABP.

This guidance does not address the development of drugs for other purposes or populations, such as treatment of community-acquired bacterial pneumonia (CABP), viral infections, or atypical bacterial pathogens (e.g., *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*). This guidance does not address pneumonia that occurs in patients living in chronic health care facilities, because bacterial etiologies may differ from HABP/VABP. This guidance does not address the development of aerosolized antimicrobial drugs.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[6]

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 facultative bacteria. Examples of etiologic pathogens of HABP/VABP include Gram-positive bacteria such as MRSA, Gram-negative Enterobacteriaceae such as *K. pneumoniae*, and Gram-negative non-Enterobacteriaceae such as *P. aeruginosa* and *Acinetobacter* species. These bacteria are often resistant to multiple antibacterial drugs, which is an increasing concern. It is also recognized that HABP/VABP may be polymicrobial.

[4] See the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[5] Beam, TR, DN Gilbert, and CM Kunin, 1992, General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products, Infectious Disease Society of America and the Food and Drug Administration, Clin Infect Dis, Nov 15 (Suppl 1): S5-S32.

[6] 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.

A synonym for HABP and VABP is *nosocomial pneumonia*. Since the FDA published a draft guidance on the development of antimicrobial drugs for the treatment of nosocomial pneumonia in 1998, there have been public discussions regarding the design of clinical trials to study HABP and VABP, including a workshop on March 31 and April 1, 2009, co-sponsored by the FDA and professional societies.[7] These discussions focused on clinical trial designs for HABP and VABP and other important issues such as the following:

- Noninferiority versus superiority trial designs
- Justification of an appropriate noninferiority margin
- Classification of the severity of illness
- Enrollment criteria
- Application of appropriate diagnostic criteria
- Use of appropriate definitions of clinical outcomes
- Timing of outcome assessments
- Use of prior antimicrobial drugs
- Use of concomitant antimicrobial drugs
- Differences and similarities between HABP and VABP

These discussions and issues have been incorporated into this draft guidance in the appropriate sections below.

III. DEVELOPMENT PROGRAM

We encourage sponsors to contact the appropriate review division to discuss specific issues that arise during the development of their drug.

A. General Considerations

1. Definition of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

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.[8]

[7] Transcripts of the March 31 and April 1, 2009, workshop, *Clinical Trial Design for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia*, can be found at http://www.fda.gov/Drugs/NewsEvents/ucm169877.htm.

[8] Oral and nasotracheal bacterial flora may not return to normal flora within 4 to 6 weeks or longer after hospitalization and some treatment guidelines describe "hospital-acquired pneumonia" as occurring within 3 months after hospital discharge. However, the goal of this guidance is to provide a definition of HABP that enriches clinical trial populations with bacterial pathogens most commonly identified in HABP and VABP, and we are defining HABP as occurring within 7 days after hospital discharge. Therefore, the definition of HABP in this guidance may differ in some respects from treatment guidelines or other clinical decision tools for consideration of antibacterial therapy.

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. Although some epidemiological studies have shown that patients with VABP may be more likely to have bacterial pathogens resistant to multiple antibacterial drugs, these pathogens have also been observed in HABP and therefore the guidance considers these two clinical disease entities together, referred to as HABP/VABP.

The more general term *health care-associated pneumonia*, or pneumonia among persons residing in chronic care facilities such as nursing homes, is not considered to be HABP as defined in this guidance because the bacterial pathogens in these patients with the broader category of health care-associated pneumonia are, in general, less likely to be similar to bacterial pathogens in patients with HABP/VABP.[9,10]

2. Nonclinical Development Considerations

New antibacterial drugs being studied for HABP/VABP should have nonclinical data documenting activity against commonly implicated pathogens for HABP/VABP (e.g., MRSA or Gram-negative Enterobacteriaceae such as *K. pneumoniae* and non-Enterobacteriaceae such as *P. aeruginosa* or *Acinetobacter* species).

Animal models of acute pneumonia have been developed and may contribute to evaluating antimicrobial 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.[11]

3. Drug Development Population

The intended clinical trial population is patients with HABP/VABP. In addition to having the clinical syndrome of bacterial pneumonia described in section III.A.1., Definition of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia, the primary analysis populations should consist of patients with bacteriological confirmation of the etiologic agent. The clinical disease spectrum of HABP/VABP in pediatric patients may be different from adults and, therefore, sponsors should discuss pediatric development with the FDA early in clinical development (e.g., the potential extrapolation of adult efficacy data to children with HABP/VABP and the appropriate pharmacokinetic and safety data in children).

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[9] The American Thoracic Society and the Infectious Disease Society of America, 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.

[10] For example, approximately 25 percent of VABP was caused by *P. aeruginosa* (the most common gram-negative pathogen causing HABP/VABP); some epidemiological information demonstrated that only 4 percent to 14 percent of health care-associated pneumonia was caused by *P. aeruginosa*.

[11] See 21 CFR 314.600.

148
149 *4. Dose Selection*
150
151 To choose the dose or doses to be evaluated in phase 3 clinical trials, sponsors should integrate
152 the findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics,
153 pharmacodynamics, safety and tolerability information from phase 1 clinical trials, and safety
154 and efficacy information from phase 2 dose-ranging clinical trials. Studies assessing drug
155 penetration at the site of action (e.g., epithelial lining fluid) can be helpful in defining doses that
156 achieve concentrations sufficient to exert an antimicrobial effect within the lungs. In addition,
157 the pharmacokinetics of the drug in specific populations (e.g., geriatric patients, patients with
158 renal and hepatic impairment) should be evaluated before initiation of phase 3 trials to determine
159 whether dose adjustments are necessary (see section III.C., Other Considerations, for
160 pharmacokinetic (PK) issues). This evaluation may help avoid the exclusion of such patients
161 from phase 3 clinical trials.
162
163 *5. Efficacy Considerations*
164
165 Either noninferiority or superiority trial designs can be used to support this indication.
166 HABP/VABP clinical trials should be designed to demonstrate a treatment effect of antibacterial
167 therapy on all-cause mortality in patients with HABP/VABP caused by bacterial pathogens (such
168 as MRSA or Gram-negative Enterobacteriaceae such as *K. pneumoniae* and non-
169 Enterobacteriaceae such as *P. aeruginosa* or *Acinetobacter* species). The primary analysis
170 population should be patients with a microbiologically confirmed bacterial etiology for
171 HABP/VABP (see section III.B.12.a., Analysis populations). If sponsors wish to include
172 additional organisms in clinical trials for this indication, they should provide data sufficient to
173 substantiate the clinical relevance of the particular organism as a pathogen in HABP/VABP.
174
175 The number of clinical trials needed to support an HABP/VABP indication depends on the
176 overall development plan for the drug under consideration. If the development plan for the drug
177 has HABP/VABP as the sole indication, then two adequate and well-controlled trials should
178 support evidence of safety and effectiveness. Because similar drug-resistant bacteria occur in
179 both HABP and VABP, and confirmation of a bacterial pathogen may be more likely to occur in
180 patients with VABP, two clinical trials that demonstrate safety and efficacy in patients with
181 VABP can provide support for an indication that encompasses both HABP and VABP. One
182 successful trial in HABP and one successful trial in VABP can provide support for an indication
183 that encompasses both HABP and VABP. Two successful trials in HABP can provide support
184 for an indication for HABP only. We recommend that patients with only VABP or only HABP
185 be enrolled in clinical trials. Microbiological diagnosis also permits analysis of treatment
186 response by individual pathogen. If a drug is being developed for other respiratory infections,
187 sponsors should discuss with the FDA whether other trials might lend support to a HABP/VABP
188 indication.
189
190 We anticipate that patients will receive an IV formulation for treatment of HABP/VABP. For
191 drugs that have both an IV and oral formulation, and when a switch to the oral formulation is
192 included in the protocol, the appropriate objective criteria that allow for the IV to oral switch
193 should be specified in the protocol and listed on the case report form. Those criteria should be

discussed with the FDA before trial initiation. The pharmacokinetics of the oral formulation should have been adequately evaluated to determine an appropriate dosing regimen and to ensure exposure comparable to the intravenous formulation.

Currently, we do not recognize any surrogate markers or clinical endpoints as substitutes for all-cause mortality outcomes in HABP/VABP trials. Sponsors who wish to propose an alternative endpoint for outcomes of HABP/VABP should discuss this with the FDA early in the drug development process.

6. Safety Considerations

The protocol should specify the methods to be used to obtain safety data during the course of the trial. Both adverse event information and safety laboratory data should be collected. All patients should be evaluated for safety at the time of each visit or assessment, regardless of whether the test drug has been discontinued. All adverse events should be followed until resolution, even if time on trial would otherwise have been completed.

A sufficient number of patients, including patients older than 65 years and patients with renal impairment, should be studied at the dose and duration proposed for use to draw appropriate conclusions regarding drug safety. Safety evaluations and assessments should take into consideration the patient populations that are likely to be treated for HABP/VABP. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations may be needed based on the nonclinical and clinical profile of the specific drug under investigation. Longer term assessment of adverse events after discontinuation or completion of the antimicrobial should be considered, depending on the specific drug's potential for long-term or delayed adverse effects.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Design

HABP/VABP trials should be randomized, double-blind, and active-controlled using a noninferiority or superiority design. Trials can include only HABP patients, only VABP patients, or patients with either HABP or VABP. However, we recommend that only HABP or only VABP patients be enrolled in trials (see section III.A.1., Definition of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia).

2. Trial Population

The trial population should include patients with HABP/VABP who are sufficiently ill that an estimate of their probable mortality within a reasonable time frame (e.g., 28 days after initiation of therapy for HABP/VABP) is approximately 20 percent or more. This can be accomplished by enrollment of an older patient population or patients with a threshold clinical severity score that predicts more severe illness or higher rate of mortality. The primary analysis population should include patients with microbiologically confirmed HABP/VABP infections caused by bacteria implicated in HABP/VABP (e.g., MRSA, Gram-negative Enterobacteriaceae such as *K.*

pneumoniae, or Gram-negative non-Enterobacteriaceae such as *P. aeruginosa* and *Acinetobacter* species) to allow assessment of the drug's effectiveness based upon the prespecified noninferiority margin, as described in section III.B.12., Statistical Considerations.

3. Entry Criteria

a. Radiographic, clinical, and microbiologic criteria

The patient should have a clinical picture of a new onset of bacterial pneumonia at a minimum of 48 hours after hospitalization or following 48 hours of mechanical ventilation, or within 7 days of discharge from a hospital, with new or evolving infiltrate(s) on chest radiograph, which is not related to another disease process.

Radiographic criteria.
The chest radiograph should show the presence of ***new*** infiltrate(s) characteristic of bacterial pneumonia. The final full report of the chest radiograph by a qualified medical professional who is not the principal investigator of the trial (e.g., a radiologist or pulmonologist masked to treatment assignment) should be included on the case report form.

Clinical criteria.
Patients should have the following clinical findings that support a diagnosis of HABP/VABP:

- Documented fever, defined as an oral or tympanic temperature greater than or equal to 38 degrees Celsius (100.4 degrees Fahrenheit), or a core temperature greater than or equal to 38.3 degrees Celsius (101 degrees Fahrenheit) or hypothermia, defined as a core body temperature of less than 35 degrees Celsius (95.2 degrees Fahrenheit); axillary temperatures are not recommended

- An elevated total peripheral white blood cell (WBC) count (WBC greater than 10,000/mm); or greater than 15 percent immature neutrophils (bands), regardless of total peripheral WBC count; or leukopenia with total WBC less than 4,500/mm

- New onset of expectorated or suctioned respiratory secretions characterized by purulent appearance indicative of bacterial pneumonia

In addition, patients with **HABP** should have at least one of the following present at enrollment:

- A new onset of cough (or worsening of baseline cough) during 48 or more hours of hospitalization or within 7 days after discharge from a hospital

- Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (e.g., dullness on percussion, bronchial breath sounds, or egophony)

- Dyspnea, tachypnea, or respiratory rate greater than 30/minute, particularly if any or all of these signs or symptoms are progressive in nature

- Hypoxemia (e.g., a partial pressure of oxygen less than 60 mm Hg while the patient is breathing on room air as determined by arterial blood gas or oxygen saturation less than 90 percent while the patient is breathing on room air as determined by pulse oximetry, or worsening of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen (PaO2/FiO2), or respiratory failure requiring mechanical ventilation)

In addition, patients with **VABP** should have a Clinical Pulmonary Infection Score of greater than 6,[12] and at least one of the following present at enrollment:

- Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (e.g., dullness on percussion, bronchial breath sounds, or egophony)

- Acute changes made in the ventilator support system to enhance oxygenation, as determined by arterial blood gas, or worsening PaO2/FiO2

We recommend using a clinical severity scoring system for the purposes of defining enrollment criteria to ensure a clinical trial population with a reasonable likelihood of predicting mortality of approximately 20 percent or greater. The protocol should provide the rationale for the use of a particular severity scoring system (e.g., Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE III, Sequential Organ Failure Assessment, Multiple Organ Dysfunction Score, or predisposition, insult, response, and organ dysfunction score) and the inclusion criteria should define a minimum score that has a reasonable likelihood of predicting mortality of approximately 20 percent or greater. For example, an inclusion criterion of patients with an APACHE II score of 15 or greater might help to predict a clinical trial population with a mortality rate of 20 percent or greater.

Microbiologic criteria.

Patients with HABP/VABP and a bacterial pathogen isolated from respiratory secretions or blood (e.g., MRSA, Gram-negative Enterobacteriaceae such as *K. pneumoniae*, or Gram-negative non-Enterobacteriaceae such as *P. aeruginosa* and *Acinetobacter* species) should be eligible for inclusion in the primary analysis population depending on the antibacterial activity of the investigational drug. At the time of enrollment before administration of clinical trial antimicrobial therapy, an adequate specimen of respiratory secretions should be obtained in all patients and sent to the laboratory for Gram stain and culture with in vitro antibacterial susceptibility testing performed on appropriate organisms isolated from the specimen. Specimens should be processed according to recognized methods.[13]

Microscopic examination of Gram stained smears should be performed. For expectorated sputum in HABP trials, specimens that have fewer than 10 squamous epithelial cells and more

[12] For example, see Pugin, J, R Auckenthaler, N Mili, et al., 1991, Diagnosis of Ventilator-Associated Pneumonia By Bacteriologic Analysis of Bronchoscopic and Non-Bronchoscopic "Blind" Bronchoalveolar Lavage Fluid, Am Rev Resp Dis, 143:1121-1129; or Singh, N, P Rogers, CW Atwood, MM Wagener, VL Yu, 2000, Short-Course Empiric Antibiotic Therapy for Patients with Pulmonary Infiltrates in the Intensive Care Unit, Am J Respir Crit Care Med, 162: 505-511.

[13] For examples, see the most current editions of the publications from American Society for Microbiology, such as *Manual of Clinical Microbiology* and *Clinical Microbiological Procedures Handbook.*

than 25 polymorphonuclear cells per low power field (100X magnification) should be considered appropriate for inclusion in evaluation of respiratory culture results. Specimens obtained from bronchial brush or endotracheal suction (VABP trials) generally should be appropriate for inclusion in evaluation of respiratory culture results (e.g., fewer than 10 squamous epithelial cells). Ten to 20 fields of the Gram stain smear also should be examined at 1,000X magnification and the morphology of potential pathogens recorded. If the specimen is kept at room temperature, the Gram stain should be performed and the specimen plated for culture within 2 hours from the collection time. Alternatively, these tests can be performed within 24 hours of collection if the specimen is stored at 2 to 8 degrees Celsius before processing.

An appropriate lower respiratory tract specimen can be obtained by any of the following modalities:

- Deep expectoration
- Endotracheal aspiration in intubated patients
- Bronchoscopy with bronchoalveolar lavage or protected-brush sampling

All isolates considered to be possible pathogens should be saved in the event that additional testing of an isolate is needed. For microbiological assessment, the investigator should describe how the sample was obtained, processed, and transported to the laboratory and identify the bacterial isolate(s). The protocol should characterize the microbiological findings based on the type of specimen collection. For example, colony counts of 10^3 colony forming units/ml (CFU/ml) can be considered a threshold for identifying pathologic bacteria from protected brush specimen whereas colony counts of 10^6 CFU/ml can be considered a threshold for identifying pathologic bacteria from an endotracheal tube specimen.

In vitro susceptibility testing should be performed on all isolates to the test drug, the comparator drug, and other antibacterial drugs that may be used to treat HABP/VABP caused by the targeted pathogens (e.g., MRSA, Gram-negative Enterobacteriaceae such as *K. pneumoniae*, or Gram-negative non-Enterobacteriaceae such as *P. aeruginosa* and *Acinetobacter* species). In vitro susceptibility tests should be performed by using standardized methods unless otherwise justified.[14] Sponsors should describe the exact methodology used for susceptibility testing if a standardized method was not used.

The following topics regarding detection of bacterial pathogens should be discussed with the FDA before trial initiation: (1) use of rapid diagnostic tests for bacterial pathogens or for respiratory viral pathogens; and (2) use of biomarkers for detection of patients with bacterial disease.

b. Exclusion criteria

In addition to complying with general exclusion criteria applicable to other trials, sponsors should exclude the following patients from HABP/VABP clinical trials:

[14] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute.

- Patients with known or suspected CABP or viral pneumonia

- Patients with acute exacerbation of chronic bronchitis without evidence of pneumonia

- Patients with tracheobronchitis

- Patients who have received prior antibacterial drugs within the past 30 days with activity against bacterial pathogens that cause HABP/VABP

- Patients with known bronchial obstruction or a history of post-obstructive pneumonia (this does not exclude patients with pneumonia who have underlying chronic obstructive pulmonary disease)

- Patients with primary lung cancer or another malignancy metastatic to the lungs

- Unless the trial is specifically designed for such a patient population, patients with cystic fibrosis, bronchiectasis, HIV/AIDS, known or suspected *Pneumocystis jiroveci* pneumonia, or known or suspected active tuberculosis

- Patients with a clinical severity score that is associated with a greatly increased probability of survival

4. Randomization, Blinding, and Stratification

Patients should be randomized to treatment groups at enrollment. To the extent possible, the test antibacterial drug and the active-controlled 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.

We recommend stratification by age and by the location in the hospital (e.g., patients admitted to a surgical intensive care unit, patients admitted to a medical intensive care unit).

5. Special Populations

The trials should include patients of both sexes and all races. If sponsors wish to include pediatric patients in HABP/VABP clinical trials, they should discuss the development plans with the FDA. Patients with renal or hepatic impairment can be enrolled provided that pharmacokinetics of the drug have been evaluated in these patients and appropriate dosing regimens have been defined (see section III.A.1., Definition of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia).

6. Choice of Comparators

Placebo-controlled trials that do not incorporate antibacterial treatment for HABP/VABP are not appropriate for this indication. The active comparator should be an antibacterial drug at the recommended dosage that is FDA-approved for treatment of "nosocomial pneumonia" or

"HABP/VABP" or is FDA-approved for the treatment of "lower respiratory tract infections" with the appropriate antibacterial spectrum for pathogens encountered in HABP/VABP. Sponsors should discuss with the FDA the choice of the control antibacterial drug if the drug is FDA-approved for "lower respiratory tract infections." Ideally, the comparator drug selected would also be a drug recommended in current treatment guidelines for HABP/VABP.

7. Prior Antibacterial Drug Use

The use of prior antibacterial drugs effective against bacteria that cause HABP/VABP should be avoided in a noninferiority trial because such treatments will reduce the difference between treatment arms and potentially bias conclusions about treatment effects. However, patients who have received prior antibacterial therapy and who are considered clinical failures on that therapy can be enrolled provided objective criteria for treatment failure are prespecified and documented on the case report form. Patients can also be enrolled if they have received prior antibacterial therapy that lacks in vitro activity against bacteria that cause HABP/VABP.

8. Concomitant Antibacterial Drugs

The broad bacterial spectrum and emerging resistance of bacterial pathogens causing HABP/VABP enhances the challenges in the design of clinical trials for this indication. An investigational drug may not fully encompass all bacterial pathogens implicated in HABP/VABP. For example, an investigational drug with in vitro activity against Gram-negative non-Enterobacteriaceae, but no activity against MRSA, can be a drug targeted for development for the treatment of HABP/VABP. Moreover, clinical trial sites may have different patterns of bacterial etiologies responsible for HABP/VABP. The protocol should specify the use of concomitant antibacterial drugs that may be permitted in the trial to provide empirical antibacterial coverage against a wide variety of pathogens, which is often necessary for initial treatment of patients with HABP/VABP before the culture results are available. Furthermore, the use of concomitant antibacterial drugs should be carefully considered in the clinical trial design, because concomitant antibacterial drugs can confound the interpretation of treatment effect in a noninferiority trial.

The investigational drug's in vitro antibacterial activity should be well-characterized, and to the extent possible, the concomitant antibacterial drug should not have antibacterial activity similar to the investigational drug to allow for the assessment of the effect of the investigational antibacterial drug. After the bacterial pathogen has been identified on culture and found on in vitro susceptibility testing to be susceptible to the investigational drug (or to the control drug used in the clinical trial), the protocol should allow for discontinuation of the concomitant antibacterial drugs (that were initially used for empirical antibacterial coverage against a wide variety of pathogens) in the setting of clinical improvement.[15] The course of treatment should be completed as monotherapy with the investigational drug or active-controlled drug, thereby enhancing the possibility of drawing stronger conclusions about an investigational drug's overall

[15] 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 in The 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.

treatment effect during a full course of treatment. The use of concomitant antibacterial drugs with similar antibacterial activity to the investigational drug or continuation of the empirical antibacterial coverage during the entire course of treatment will compromise the ability to evaluate the treatment effect of an investigational drug.

9. Efficacy Endpoints

The recommended primary endpoint is all-cause mortality within 28 days after randomization.

- Clinical success: patients alive within 28 days after randomization into the clinical trial.

- Clinical failure: patients who have died within 28 days after randomization into the clinical trial.[16]

Generally in HABP/VABP trials, there is no need for primary endpoint adjudication. Secondary endpoints can include outcomes as follows:

- All-cause mortality within 14 days after randomization

- Clinical cure: complete resolution of HABP/VABP signs and symptoms present at enrollment, no new symptoms or complications attributable to HABP/VABP, and alive at 28 days

- Clinical improvement: respiratory rate, heart rate, and temperature recordings at baseline compared to 3 to 5 days of therapy and compared to the end of therapy; time to resolution of HABP/VABP signs and symptoms present at enrollment; or improvement in PaO2/FiO2 over time

- Clinical progression: lack of resolution or worsening of HABP/VABP signs and symptoms present at enrollment and alive at 28 days; administration of rescue antibacterial therapy and alive at 28 days; or administration of antibacterial therapy for another bacterial infection and alive at 28 days

Any endpoint that includes symptom response should use a patient-reported outcome (PRO) measurement for symptom assessment. PRO tools can also be used to assess signs or aspects of functioning that are appropriately assessed by the patient themselves. PRO tools can be self-administered or interviewer-administered, if necessary, using an established script for the interview where the interviewer records only those responses given by the patient. If a PRO tool

[16] Among the studies of HABP/VABP that were evaluated, the exact timing of the follow-up for all-cause mortality was not reported (see Appendix A). The choice of the timing of the endpoint at 28 days after randomization appears to be clinically meaningful and assumes the duration of antibacterial therapy at approximately 2 weeks. Sponsors can discuss with the FDA an alternative timing of the all-cause mortality primary endpoint based on the total duration of administration of trial drugs (e.g., all-cause mortality from the beginning of therapy to 14 days after completion of therapy).

is used, its content validity and other measurement properties should be demonstrated in the population represented in the clinical trial.[17]

Sponsors should be aware that we consider analyses of secondary and additional endpoints to be exploratory, because trials usually are not designed to address the multiplicity questions raised by these analyses. It is possible, however, to identify in the statistical analysis plan the particular analyses and subsets of interest when the trial is successful on its primary endpoint, and, using sequential approaches or multiplicity corrections, reach statistically valid conclusions on secondary endpoints. Analyses of secondary and additional endpoints is often most helpful for identifying areas for study in future trials.

10. Trials in HABP/VABP Patients With Unmet Need

HABP/VABP patients with unmet need (e.g., patients who have or are suspected of having a bacterial pathogen with in vitro susceptibility testing that shows resistance to most antibacterial drugs) may not be appropriate patients for enrollment in a noninferiority trial design (see section III.B.9., Efficacy Endpoints). The noninferiority trial design assumes that the active-controlled drug has a known and reliable treatment effect. Furthermore, antibacterial drug therapy is usually chosen for each individual patient based on the results of in vitro susceptibility testing. Thus, the use of the same control antibacterial drug in a noninferiority trial may not be appropriate for these patients (e.g., if a patient's infectious bacteria are resistant to the control drug).

An active-controlled trial designed to show superiority can be considered in the setting of HABP/VABP caused by bacteria resistant to multiple antibacterial drugs. Such a trial may also enroll patients with a greater degree of comorbid conditions or may be appropriate in the setting where the risk-benefit profile of the drug only supports a more limited use because of its toxicity. Furthermore, important information about a drug's pharmacokinetic/pharmacodynamic (PK/PD) properties can be evaluated in patients with a greater degree of comorbid conditions. The following three conceptual approaches can be considered for superiority clinical trial designs:

1. Patients would be randomized to receive either the investigational drug or antibacterial drug treatment chosen empirically or based on in vitro susceptibility testing when available. The evaluation of efficacy of the investigational drug would be based on a finding of superiority in the group that received the investigational drug versus the group that received the chosen antibacterial drug treatment.

2. All patients would receive antibacterial drug treatment chosen empirically or based on the results of in vitro susceptibility testing when available, and patients would be randomized to receive an investigational drug or matching placebo. The evaluation of efficacy of the investigational drug would be based on a finding of superiority in the group that received the investigational drug plus the chosen antibacterial drug treatment versus the group that received placebo plus the chosen antibacterial drug treatment.

[17] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

3. Patients would be enrolled in a dose-response trial where two doses for which there is equipoise are compared with the goal of showing superiority in one dose group versus the other dose group.

We encourage sponsors considering superiority clinical trial designs in HABP/VABP patients with unmet need (e.g., HABP/VABP caused by bacteria resistant to multiple antibacterial drugs) to discuss the design with the FDA during protocol development.

11. Trial Procedures and Timing of Assessments

a. Entry visit

At the entry visit, the following information should be captured and recorded on the case report form:

- History and physical examination
- Prior and concomitant drugs
- Baseline clinical signs and symptoms including vital signs
- Chest x-ray or other radiographic imaging of the chest
- Clinical severity score(s)
- Microbiologic specimens: Adequate respiratory specimens as determined by Gram stain, culture of an appropriate respiratory specimen, and blood cultures (using aseptic techniques, aerobic and anaerobic blood cultures obtained from two separate venipuncture sites before administration of antibacterial therapy)
- Laboratory tests as appropriate
- Ventilator settings as appropriate

b. On-therapy visit at days 2 to 4 after enrollment

Patients should be evaluated early in the course of treatment to assess for clinical failure, where rescue antibacterial drug therapy is appropriate, or clinical improvement. This visit should capture clinical observations such as vital signs, physical examination findings, laboratory test results, changes in ventilator settings, supplemental oxygen requirements, microbiology results, or chest x-ray findings. The de-escalation of antibacterial drug therapy should be documented at this visit, as appropriate.

c. Other on-therapy visits

It is important that investigators distinguish between patients who are worsening or not improving (i.e., where antibacterial rescue therapy is appropriate) from patients who are slow to improve but may still remain on assigned therapy and thereby achieve clinical success. Specific objective criteria to initiate rescue therapy should be included in the protocol and should be documented as a study visit, including the collection of a specimen for microbiology assessments (see section III.B.3.a., Radiographic, clinical, and microbiologic criteria).

d. End-of-therapy visit

Patients should be evaluated clinically at the end of the prescribed therapy. Laboratory assessments for safety should be performed at this visit. If the trial drug needs to be continued beyond the protocol-specified duration, objective criteria for extending the therapy should be prespecified in the protocol. Patients without clinical improvement or with progression of signs and symptoms should be considered as having clinical progression and alternative antibacterial rescue therapy should be provided.

e. Day 28 visit

Patients should be assessed in the hospital, in the clinic, by telephone, or by other interactive technology at day 28 for documentation of the all-cause mortality primary endpoint. Although the attribution of the cause of death by the investigator or sponsor may be informative for exploratory endpoints, the primary endpoint is all-cause mortality regardless of the cause of death.

12. Statistical Considerations

The trial's primary and secondary hypotheses and the analysis methods should be prespecified in the protocol and in the statistical analysis plan, and should be finalized before trial initiation. The primary endpoint analysis should be a comparison of all-cause mortality at 28 days after randomization in the clinical trial between test and active-controlled treatment groups. We recommend that the trials be adequately powered to compare all-cause mortality rates between treatment groups. If sponsors choose to test multiple primary or secondary hypotheses, they should address issues related to the potential inflation of false-positive results and control of overall type I error rate caused by multiple comparisons.[18]

a. Analysis populations

The following definitions apply to various analysis populations in HABP/VABP clinical trials:

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

[18] These issues should be discussed with the FDA during protocol development, and if any subsequent changes are considered, they should be discussed with the FDA before incorporation into the statistical analysis plan. See ICH E9 and ICH E10.

- The microbiological intent-to-treat population (MITT population) — All randomized patients who have a baseline bacterial pathogen that causes HABP/VABP against which the investigational drug has antibacterial activity. This includes bacterial pathogens associated with HABP/VABP identified in blood or appropriate sputum specimen (e.g., MRSA, Gram-negative Enterobacteriaceae such as *K. pneumoniae*, or Gram-negative non-Enterobacteriaceae such as *P. aeruginosa* and *Acinetobacter* species). Patients should not be excluded from this population based upon events that occur post-randomization (e.g., loss to follow-up).[19]

- Clinically evaluable or per-protocol populations — Patients who meet the definition for the ITT population and who follow important components of the trial as specified in the protocol.

- Microbiologically evaluable populations — Patients who meet the definition for the MITT population and who follow important components of the trial as specified in the protocol.

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

The MITT population should be considered the primary analysis population. Consistency of the results should be evaluated in all populations and any inconsistencies in the results of these analyses should be explored and explanations should be provided in the complete study report.

b. Noninferiority margins

A noninferiority clinical trial design with a prespecified noninferiority margin can be used in the evaluation of a test antibacterial drug for HABP/VABP. The noninferiority margin can be justified based on historical evidence of the sensitivity to drug effect (HESDE) of antibacterial therapy on all-cause mortality in patients with HABP/VABP. Based on a recent review of historical evidence of treatment effects and with an estimate of all-cause mortality in the control group of approximately 20 percent or greater, an M1 is conservatively estimated at 20 percent and a noninferiority margin of 10 percent is recommended to preserve the treatment effect on all-cause mortality evaluated 28 days after randomization.[20]

If the 28-day all-cause mortality rate in the active-controlled group is lower than approximately 20 percent, an approach using the odds ratio metric should be used as the measure for assessing treatment effects. The constancy assumption may not be valid for all-cause mortality rates lower than approximately 20 percent in the control group in a noninferiority trial (see Appendix A); sponsors considering using the odds ratio should discuss their plans with the FDA when their

[19] The attribution of efficacy to an investigational drug would be compromised if a bacterial pathogen has in vitro susceptibility to both the investigational drug and a concomitant drug used for initial empirical antibacterial coverage. Sponsors should address this issue in the protocol, for example, by choosing concomitant antibacterial drugs that do not have overlapping antibacterial activity with an investigational drug, or by excluding patients from the MITT population with baseline pathogens susceptible to both the investigational drug and a concomitant drug.

[20] See Appendix A and Sorbello, A, S Komo, T Valappil, 2010, Noninferiority Margin for Clinical Trials of Antibacterial Drugs for Nosocomial Pneumonia, Drug Inf J, 44(2):165-176.

protocol is being developed.[21] Sponsors should justify the noninferiority margin for the proposed trial design and patients enrolled. For clinical trials with observed active control mortality rate of less than 20 percent, a fixed noninferiority margin of 1.67 based on an odds ratio metric should be used. When the trial is completed, the applicability of the HESDE to the actual patient population enrolled in the trial should be assessed in the final clinical trial report.

c. Sample size

The appropriate sample size for a clinical trial should be based upon the number of patients needed to answer the prespecified hypothesis posed by the trial. The sample size is influenced by several factors, including the prespecified type I and type II error rates, estimate of the control mortality rate, the noninferiority margin, or the magnitude by which the trial drug is expected to be superior (for a superiority trial). The appropriate sample size should be estimated using a two-sided α=0.05.

d. Missing data

There is no optimal way to deal with missing data from clinical trials. Sponsors should make every attempt to limit loss of patients from the trial. Analyses that exclude patients are subgroup analyses, and patients who do not complete the trial may differ substantially from patients who remain in the trial in both measured and unmeasured ways. The method of how missing data will be handled should be specified in the protocol. Interpretation of trial results may be affected if there are missing data. Missing data should be minimal in clinical trials using all-cause mortality as a primary endpoint.

e. Interim analyses and data monitoring committee

If interim effectiveness analyses for success or futility will be performed, they should be prespecified in the protocol and in the analysis plan along with a justification. Details on the operating procedures also should be provided before trial initiation. The purpose of the interim analysis should be stated along with the appropriate statistical adjustment to control the overall type I error rate. It is important that an appropriate firewall be in place to guarantee that the interim analysis will not affect trial conduct and thereby compromise trial results. This can be accomplished by creating an independent data monitoring committee (DMC) that monitors the protocol with prespecified operational procedures. Such a committee also might be created if there were safety concerns about the drug or the treatment approach. If a DMC is used, a detailed charter with the composition of the committee members, conflicts of interest, decision

[21] All-cause mortality rates depend on the severity of disease and underlying patient characteristics. We evaluated all-cause mortality rates observed in recently conducted clinical trials submitted for review, which varied between 8 percent to 28 percent (see Sorbello, A, S Komo, T Valappil, and S Nambiar, 2010, Registration Trials of Antibacterial Drugs for the Treatment of Nosocomial Pneumonia, Clinical Infectious Diseases, 51 (S1): S36 – S41). The reasons for the large variability in all-cause mortality rates are not entirely clear, but in general the trials that enrolled a greater proportion of patients with VABP or trials that enrolled patients with a greater likelihood of a mortality outcome had all-cause mortality rates of approximately 20 percent or greater.

rules, details on the measures taken to protect operational bias and the integrity of the trial, and the standard operating procedures should be provided for review.[22]

f. Secondary analyses

Sponsors can present secondary analyses on other endpoints of interest. An analysis of patients who initiate rescue antibacterial drug therapy between the treatment groups is a recommended secondary endpoint; imbalances between treatment groups in the proportion of patients who initiate rescue antibacterial drug therapy can be an important consideration for overall efficacy. Sponsors can present secondary analyses on other endpoints of interest that can include but not be limited to the following:

- Evaluation of internal consistency of the results using responses based on patient demographic characteristics, such as age, sex, geographic region, underlying medical conditions, and microbiological etiology

- Time to mortality analysis by treatment group (e.g., Kaplan-Meier method)

g. Statistical analysis plan

Before initiation of any phase 3 trial, sponsors should provide a detailed statistical analysis plan with the protocol for the phase 3 trial.

C. Other Considerations

1. Pharmacokinetic/Pharmacodynamic Considerations

The PK/PD of the drug should be thoroughly evaluated. The results from nonclinical PK/PD assessments should be integrated with the findings from phase 1 PK studies to help identify the appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical trials.

Consideration should be given to obtaining sparse samples from all patients in phase 2 and phase 3 clinical trials to allow for the estimation of drug exposure in each patient. Collection of PK data in phase 2 clinical trials can be used to explore the exposure-response relationship and to confirm that the proper dosing regimen is selected for further evaluation in phase 3. Collection of PK data in phase 3 clinical trials may help to resolve any potential questions regarding efficacy or safety that arise from the clinical trials.

A retrospective exposure-response analysis based on the population PK model might help to assess the relationship between PK/PD indices and observed clinical and microbiologic outcomes. The relationship between drug exposure and clinically relevant adverse events should also be explored to identify potential risks with different dosing regimens (if applicable) and specific patient populations.

[22] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

745 *2. Labeling Considerations*
746
747 The labeled indication should reflect the patient population enrolled in the clinical trials. Two
748 successful trials in patients with VABP would support a labeled indication for treatment of both
749 HABP and VABP. One successful trial in HABP patients and one successful trial in VABP
750 patients would support a labeled indication for treatment of both HABP and VABP. Two
751 successful trials in patients with HABP would support a labeled indication for treatment of
752 HABP.
753
754 *3. Risk-Benefit Considerations*
755
756 Risk-benefit considerations depend on the population being studied and the safety profile of the
757 drug being investigated. For example, in areas where a drug demonstrates meaningful
758 therapeutic advantage in patients with unmet needs, a greater degree of risk or uncertainty may
759 be offset by the benefit provided in an overall evaluation of risk and benefit.
760

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

A clinical trial design using an active-comparator antibacterial drug is recommended for the evaluation of a test antibacterial drug in clinical trials of HABP/VABP. One type of active-controlled trial is the noninferiority trial. The principles of the noninferiority clinical trial design and defining an appropriate noninferiority margin are described in ICH E10 and guidances for industry.[23] The finding of noninferiority demonstrates that the test drug is not worse than the active-comparator drug by a specified acceptable amount, or noninferiority margin. An important first step in the justification of a noninferiority margin is an understanding of the treatment effect of the active-comparator drug that can be reliably distinguished from placebo (M1). This information is usually derived from previously conducted placebo-controlled trials; however, no placebo-controlled trials have been conducted that enrolled patients with HABP/VABP. Therefore, this appendix describes an approach to provide historical evidence of sensitivity to drug effect and support M1 by using studies identified from a literature review that were not placebo-controlled studies. Sponsors should use the information contained in this appendix when considering the justification for a noninferiority margin in active-controlled trials for treatment of HABP/VABP designed for noninferiority.

Historical Evidence of Sensitivity to Drug Effects

Placebo-controlled trials provide the most direct estimate of an active-comparator drug's treatment effect. In the absence of placebo-controlled trials, as in the case of HABP/VABP, additional data from other studies including observational studies or active-controlled trials can be used to evaluate a comparator drug's treatment effect. Another aspect that pertains to historical evidence is the constancy assumption. That is, are there reliable data that a comparator drug's treatment effect would not differ between studies conducted today and studies conducted previously?

A literature search was performed to identify published studies with keywords and synonyms related to HABP/VABP. Examples of keywords used include *nosocomial pneumonia* and *ventilator-associated pneumonia*. In addition, because of multidrug resistance and use of an antibacterial therapy to which a bacterial pathogen is resistant might be considered similar to a *placebo* effect, keywords related to inappropriate antibacterial therapy in hospitalized patients with pneumonia were used in a search. Examples of keywords used include *inadequate therapy* and *delayed initiation*. Finally, publications describing the effects of antibacterial drugs that are recommended in treatment guidelines for HABP/VABP were reviewed.

A total of 36 relevant publications were identified that provided data on all-cause mortality and clinical response criteria in patients with HABP/VABP. However, 16 publications did not

[23] See the guidance for industry *Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval* and the draft guidance for industry *Non-Inferiority Clinical Trials*. 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 Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. ICH guidances can also be found on this Web site.

distinguish the mortality or clinical outcome data among the subgroups of patients in the ITT population or in different populations (i.e., inappropriate versus appropriate antibacterial therapy). Twenty publications were identified as having sufficient data for inclusion in the analysis to evaluate the HESDE. The entry criteria for each study included patients with a pulmonary infiltrate on chest radiography in addition to fever, leukocytosis, and purulent respiratory tract secretions. A total of 14 publications were observational studies among patients that received either appropriate antibacterial treatment or inadequate treatment (e.g., patients receiving antibacterial therapies that were later found to be resistant to the bacterial pathogen). Six studies were randomized, prospective, active-controlled efficacy studies for the evaluation of drugs for treatment of HABP or VABP.

HESDE was not based on the within-study differences reported between appropriate compared to inadequate, delayed, or inappropriate initial antibacterial therapy in the historical observational studies for two reasons. First, the dosing or duration of appropriate antibacterial treatment regimens was not specified in any of the reports, so that we could not confirm that treatment regimens designated as adequate therapy actually represented the best antibacterial treatment available for HABP and VABP at the time the studies were conducted. Second, there were substantial within-study disparities with respect to age, severity of illness (e.g., APACHE II scores), and baseline pathogens, which are important measured baseline characteristics that can potentially affect the risk for death independent of the adequacy of the administered antibacterial drugs. Additionally, because the studies were nonrandomized, we were concerned about confounding caused by an unequal distribution of unmeasured prognostic factors associated with mortality across treatment arms within each study that can also affect the risk for death independent of the adequacy of the administered antibacterial drugs. Thus, it was necessary to base HESDE on cross-study comparisons. When conducting cross-study comparisons, it is critical that the active-comparator and inadequate, delayed, or inappropriate treatment groups be similar in terms of baseline demographics, severity of illness, and any other factors that can affect mortality. For this reason, a subset of only seven of the studies was used to estimate the HEDSE.

Studies in Patients Who Received Inadequate, Delayed, or Inappropriate Treatment for HABP/VABP

The 14 studies that reported outcomes among patients that received inadequate treatment were reviewed for an estimate of all-cause mortality in the inadequate, delayed, or inappropriate treatment groups.[24] Clinical responses were not provided in a standardized or consistent manner in many of these studies, and therefore clinical responses cannot be *pooled* into an estimate of the treatment effect. Because all-cause mortality was identified from each of these studies, an estimate of all-cause mortality in inadequate, delayed, or inappropriately treated patients can be determined. Two retrospective studies described a small number of patients left untreated, but did not provide demographic characteristics or clear explanations for why these patients were left untreated. The other 12 studies were used in the estimation of an all-cause mortality rate in inadequate, delayed, or inappropriately treated patients. The studies showed variations in population sizes from 65 to 430 patients. Demographic characteristics differed among the studies, with mean APACHE II scores varying from 17.2 to 26.2 and mean ages varying from 42

[24] See Appendix B for a listing of the 14 studies.

years to 67 years. An exact time period for the reporting of all-cause mortality was not specified in the studies; seven studies did not specify a time period at all and the other studies reported all-cause mortality during hospitalization or included some period of time after discharge from an intensive care unit (ICU) setting or from a hospital. The amount of time spent in an ICU or hospital can vary widely among different patients, so it was not possible to identify a specific time point after initiation of treatment in an estimate of all-cause mortality.

The point estimate of all-cause mortality among inadequate, delayed, or inappropriately treated patients in the studies varied from 35 percent to 92 percent. Table 1 depicts the results of the 14 studies.

Table 1. Nonrandomized Clinical Studies Involving Inadequate, Delayed, or Inappropriate Therapies in Hospitalized Patients With Nosocomial Pneumonia Used to Estimate the All-Cause Mortality Rate

Study/First Author	Number of Patients With Nosocomial Pneumonia (% VAP)	Inappropriate Treatment Group All-Cause Mortality n/N (%)	Appropriate Treatment Group All-Cause Mortality n/N (%)	Reporting Time Period for All-Cause Mortality
Alvarez-Lerma	430 (not reported)	51/146 (35%)	92/284 (32%)	72 hours after ICU discharge
Celis	118 (71%)	11/12 (92%)	33/108 (31%)	Not reported
Iregui	107 (100%)	23/33 (70%)	21/74 (28%)	During hospitalization
Kollef	130 (100%)	31/51 (61%)	17/51 (33%)	Not reported
Leone	115 (100%)	7/15 (47%)	20/100 (20%)	Not reported
Leroy	132 (100%)	16/26 (62%)	42/106 (40%)	Deaths at ICU discharge
Luna 2006	76 (100%)	33/52 (64%)	7/24 (29%)	28-days after VAP onset
Luna 2003	63 (100%)	9/13 (69%)	23/50 (46%)	28-days during hospitalization
Luna 1997	65 (100%)	40/49 (82%)	6/16 (38%)	During hospitalization
Rello	121 (100%)	5/11 (45%)	34/110 (31%)	Not reported
Smith	85 (not reported)	5/8 (62%)	37/77 (48%)	Not reported

continued

862 *Table 1, continued*

Study/First Author	Number of Patients With Nosocomial Pneumonia (% VAP)	Inappropriate Treatment Group All-Cause Mortality n/N (%)	Appropriate Treatment Group All-Cause Mortality n/N (%)	Reporting Time Period for All-Cause Mortality
Stevens	75 (not reported)	20/34 (59%)	33/41 (80%)	Not reported
Teixeira	151 (100%)	35/69 (51%)	24/82 (29%)	28-days after VAP onset
Torres	78 (100%)	14/27 (52%)	12/51 (23%)	Not reported
DerSimonian and Laird random effects meta-analysis for the all-cause mortality rate from all studies in inappropriate, delayed, or inadequately treated patients			60% (95% CI 49%, 69%)	
Kollef and **Luna 2006:** DerSimonian and Laird random effects meta-analysis for the all-cause mortality rate in inappropriate, delayed, or inadequately treated patients			62% (95% CI 52%, 71%)	

863
864 The data from all 14 studies were used in a DerSimonian and Laird random effects meta-analysis
865 that yielded an estimate of all-cause mortality of 60 percent (95 percent CI 49 percent, 69
866 percent) for inadequate, delayed, or inappropriately treated patients.[25] It was noted that most of
867 the studies were single-center or had missing demographic characteristics that provided
868 limitations on the ability to interpret the all-cause mortality data. In general, for each study all-
869 cause mortality was lower in the patients that received appropriate therapy in comparison to the
870 patients that received inadequate, delayed, or inappropriate therapies. Two studies were
871 identified where patients had similar demographic characteristics and similar clinical severity
872 scores to three of the studies identified among the active-controlled treatment studies.[26] An
873 analysis of all-cause mortality based on patients receiving inappropriate therapies for nosocomial
874 pneumonia or ventilator-associated pneumonia in these two studies was deemed most
875 appropriate. A DerSimonian and Laird random effects meta-analysis of all-cause mortality in
876 these two studies yielded an **estimate of all-cause mortality for inadequate, delayed, or**
877 **inappropriate therapy in HABP/VABP of 62 percent (95 percent CI 52 percent, 71**
878 **percent)**.
879

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

[26] Kollef, MH and S Ward, 1998, Chest, 113:412-420; and Luna, CM, P Aruj, MS Neiderman, et al., 2006, Eur Respir J, 27:158-164.

Controlled Studies of HABP/VABP

The mortality rate for an active-comparator antibacterial drug was evaluated by examining studies reporting mortality among patients with HABP/VABP treated with antibacterial drugs recommended in current guidelines for treatment by the American Thoracic Society/Infectious Disease Society of America. Eight studies were found that evaluated the antibacterial drugs considered appropriate for initial treatment for HABP/VABP: piperacillin/tazobactam, imipenem, ceftazidime, ciprofloxacin, levofloxacin, vancomycin, and linezolid.[27] The demographic characteristics including age, mean APACHE II scores, and duration of antibacterial treatment showed some variability among the eight studies. Although clinical responses were reported in these studies, only all-cause mortality was evaluated as a treatment effect because the reporting of clinical response endpoints was not standardized across the studies. Three studies were open-label and five studies were double-blind. Several of the studies included an aminoglycoside antibiotic for additional Gram-negative bacterial coverage. A limitation of these studies is the concomitant administration of an aminoglycoside antibiotic; the actual treatment effect of an individual antibacterial drug may be overestimated.

Among the groups of patients treated with these different antibacterial drugs, the point estimates of the reported mortality rates were between 8 percent and 31 percent, as depicted in Table 2.

Table 2. Prospective, Controlled Clinical Trials in Nosocomial Pneumonia Used to Estimate the Treatment Effect of a Control Antibacterial Drug

Study/First Author	Number of Patients With Nosocomial Pneumonia (% VAP)	Treatment Group* 1 All-Cause Mortality n/N (%)	Treatment Group* 2 All-Cause Mortality n/N (%)	Reporting Time Period for All-Cause Mortality
Alvarez-Lerma	124 (85.5%)	P/T/A 27/88 (31%)	Cef/A 8/36 (22%)	Not reported
Brun-Buisson	197 (64.5%)	P/T/A 18/98 (18%)	Cef/A 22/99 (22%)	28-days post-randomization
Fink	402 (75.6%)	Imi 38/200 (19%)	Cip 43/202 (21%)	30 days after completion of therapy
Joshi	437 (69.1%)	P/T/To 23/222 (10%)	Imi/To 17/215 (8%)	Not reported
Schmitt	217 (23.5%)	P/T 17/107 (16%)	Imi 11/110 (10%)	Not reported
West	438 (10.7%)	Imi/Cip 32/218 (15%)	Lev/Lev PO 38/220 (17%)	28-32 days after completion of therapy

continued

[27] See Appendix B for the studies that evaluate the antibacterial drugs considered appropriate for initial treatment.

Table 2, continued

Study/First Author	Number of Patients With Nosocomial Pneumonia (% VAP)	Treatment Group* 1 All-Cause Mortality n/N (%)	Treatment Group* 2 All-Cause Mortality n/N (%)	Reporting Time Period for All-Cause Mortality
Rubinstein	396 (57.3%)	Lin/Az 36/203 (18%)	Van/Az 49/193 (25%)	12-28 days after completion of therapy
Wunderink	623 (50.6%)	Lin/Az 64/321 (20%)	Van/Az 61/302 (20%)	15-21 days after completion of therapy
Alvarez-Lerma, **Fink**, **West, Rubinstein, and Wunderink:** DerSimonian and Laird random effects meta-analysis for a rate of all-cause mortality in an active control			20% (95% CI 18%, 23%)	

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

As noted above, there was some variability in demographic characteristics among the studies. Five studies[28] appeared to have similar patient demographic characteristics and clinical disease severity scores to the two studies[29] identified among the inadequately, delayed, or inappropriately treated groups. These studies were considered to be the most appropriate to use in an estimate of an active-controlled all-cause mortality rate, following treatment with piperacillin/tazobactam, imipenem/cilastatin, ceftazidime, ciprofloxacin, or levofloxacin. A DerSimonian and Laird random effects meta-analysis of all-cause mortality in these five studies yielded an **estimate of all-cause mortality for an active-comparator antibacterial drug of 20 percent (95 percent CI 18 percent, 23 percent)**.

Summary and Determination of Noninferiority Margin for HABP/VABP

The available data from seven studies with similar patient populations allow an estimate of the effect of inadequate,[30] delayed, or inappropriate therapies and an estimate of the effect of appropriate antibacterial active-controlled drugs. The difference between the two estimates can

[28] Alvarez-Lerma, F, J Insausti-Ordenana, R Jorda-Marcos, et al., 2001, Intensive Care Med, 27:493-502; Fink, MP, DR Snydman, MS Neiderman, et al., 1994, Antimicrob Agents Chemother, 38:547-557; West, M, BR Boulanger, C Fogarty, et al., 2003, Clin Ther, 25:485-506; Rubinstein, E, SK Cammarata, TH Oliphant, et al., 2001, Clin Infect Dis, 32:402-412; Wunderink, RG, SK Cammarata, TH Oliphant, et al.,2003, Clin Ther, 25:980-992.

[29] Kollef, MH and S Ward, 1998, Chest, 113:412-420; Luna, CM, P Aruj, MS Neiderman, et al., 2006, Eur Respir J, 27:158-164.

[30] Kollef, MH and S Ward, 1998, Chest, 113:412-420; Luna, CM, P Aruj, MS Neiderman, et al., 2006, Eur Respir J, 27:158-164; Alvarez-Lerma, F, J Insausti-Ordenana, R Jorda-Marcos, et al., 2001, Intensive Care Med, 27:493-502; Fink, MP, DR Snydman, MS Neiderman, et al., 1994, Antimicrob Agents Chemother, 38:547-557; West, M, BR Boulanger, C Fogarty, et al., 2003, Clin Ther, 25:485-506; Rubinstein, E, SK Cammarata, TH Oliphant, et al., 2001, Clin Infect Dis, 32:402-412; Wunderink, RG, SK Cammarata, TH Oliphant, et al.,2003, Clin Ther, 25:980-992.

be used to help understand an active-controlled drug's treatment effect over inadequate, delayed, or inappropriate therapies (M1). The all-cause mortality rate was 62 percent (95 percent CI 52 percent, 71 percent) for patients treated with inadequate, delayed, or inappropriate therapies and the all-cause mortality rate was 20 percent (95 percent CI 18 percent, 23 percent) for patients treated with an active-controlled drug. Although the DerSimonian and Laird model accounts for some of the variability of the data, it is still appropriate to remain conservative when considering an estimate of M1. Therefore, the lower bound of the 95 percent CI for the treatment effect of inadequate, delayed, or inappropriate therapies minus the upper bound of the 95 percent CI for an estimate of the treatment effect of an active-comparator antibacterial drug results in an estimate of the treatment effect of an antibacterial drug over inadequate, delayed, or inappropriate therapies of approximately 29 percent (52 percent *minus* 23 percent). This estimate of M1 from HESDE has several limitations as described below:

- There are no placebo-controlled studies in the historical literature
- The HESDE for treatment of HABP/VABP was derived from only seven studies: two studies for the estimate of the effect of inadequate, delayed, or inappropriate therapies and five studies for the estimate of the effect of appropriate therapy
- Some of the studies were open-label comparisons or observational studies leading to the potential for bias; only three studies incorporated double-blinded randomization
- There was variability in baseline patient demographics and disease severity across the studies
- The studies assessed mortality at different time points or did not state when mortality was assessed
- The cross-study comparisons to arrive at estimates of all-cause mortality rates create uncertainties: the all-cause mortality rates were higher in the appropriately treated groups for the studies that were used in the estimate of the treatment effect of inadequate, delayed, or inappropriate therapies (see Table 1) in comparison to the all-cause mortality rates in the active-controlled studies that were used in the estimate of the treatment effect of appropriate therapy (see Table 2)
- Technological advances over time in the management of patients in intensive care units may lead to variability in the estimates of all-cause mortality rates in the historical studies.

One of the strategies employed in choosing the margin M1 for the noninferiority study design is that of *discounting* or reducing the magnitude of the margin size that is used in the noninferiority study from what is calculated from the analysis of HESDE. Such discounting is done to account for the uncertainties in the assumptions that need to be made in estimating, based on past performance, the effect of the active control. This concept of discounting focuses on M1 determination and is distinct from a clinical judgment that the effect that can be lost on clinical grounds should be some fraction of M1 (i.e., M2). Given the limitations and uncertainties listed

above, the treatment effect should be further discounted to determine M1. To account for these limitations and uncertainties, the treatment effect of 29 percent was discounted by an additional 30 percent to arrive at an M1 of 20 percent. **Thus, a conservative and reliable estimate of the treatment effect on all-cause mortality of an antibacterial drug against placebo (M1) in the treatment of HABP/VABP is approximately 20 percent.**

The noninferiority clinical trial should demonstrate similarity to the historical studies used to estimate the treatment effect (the constancy assumption) based on a patient population with approximately 20 percent all-cause mortality rate in the active treatment groups. As such, the active-controlled drug should have an all-cause mortality rate of approximately 20 percent (see Table 2) to maintain the constancy assumption in noninferiority clinical trials. If the active control all-cause mortality rate is less than approximately 20 percent, an odds ratio can be considered as a measure for assessing treatment effects. However, the constancy assumption may not be valid for an all-cause mortality rate of less than 20 percent in the active-control group. Sponsors considering using the odds ratio as a measure for assessing treatment effects should discuss their plans with the FDA during clinical development.

In addition to the scientific and statistical justifications, the prespecified amount by which a test antibacterial drug is allowed to be inferior should also be subject to clinical judgment. A large proportion of M1 should be preserved to be clinically acceptable with respect to the efficacy of a test drug on the endpoint of all-cause mortality. **A noninferiority margin of 10 percent is recommended to preserve the treatment effect of antibacterial drug therapy in a noninferiority clinical trial that enrolls patients with HABP or VABP. All-cause mortality within 28 days after randomization in the active-control group should be approximately 20 percent or greater to preserve the constancy assumption. All-cause mortality should be the primary endpoint at 28 days after randomization.**

APPENDIX B: LISTINGS OF LITERATURE REVIEWED FOR HISTORICAL EVIDENCE

The 14 studies reviewed for an estimate of the effect of inadequate, delayed, or inappropriate treatment for HABP/VABP (listed in alphabetical order):

- Alvarez-Lerma, F and the ICU-Acquired Pneumonia Study Group, 1996, Modification of Empiric Antibiotic Treatment in Patients With Pneumonia Acquired in the Intensive Care Unit, Intensive Care Med, 22:387-394.

- Celis, R, A Torres, JM Getell, et al., 1988, Nosocomial Pneumonia: A Multivariate Analysis of Risk and Prognosis, Chest, 93(2):318-324.

- Iregui, M, S Ward, G Sherman, VJ Fraser, and MH Kollef, 2002, Clinical Importance of Delays in the Initiation of Appropriate Antibiotic Treatment of Ventilator-Associated Pneumonia, Chest, 122:262-268.

- 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.

- Leone, M, F Carcin, J Bouvenot, et al., 2007, Ventilator-Associated Pneumonia: Breaking the Vicious Circle of Antibiotic Overuse, Crit Care Med, 35:379-385.

- Leroy, O, A Meybeck, T d'Escrivan, et al., 2003, Impact of Adequacy of Initial Antimicrobial Therapy on the Prognosis of Patients With Ventilator-Associated Pneumonia, Intensive Care Med, 29:2170-2173.

- 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.

- Luna, CM, D Blanzaco, MS Neiderman, et al., 2003, Resolution of Ventilator-Associated Pneumonia: Prospective Evaluation of the Clinical Pulmonary Infection Scores as an Early Clinical Predictor of Outcome, Crit Care Med, 31:676-682.

- Luna, CM, P Vujacich, MS Neiderman, et al., 1997, Impact of BAL Data on the Therapy and Outcome of Ventilator-Associated Pneumonia, Chest, 111:676-685.

- Rello, J, L Vidaur, A Sandiumenge, et al., 2004, De-Escalation Therapy in Ventilator-Associated Pneumonia, Crit Care Med, 32:2183-2190.

- Smith, IM, MC Champion, EC Hazard, L Lowry, PE Leaverton, 1970, Single and Combined Antibiotics in the Treatment of Pseudomonas Aeruginosa Infections, In: Progress in Antimicrobial and Anticancer Chemotherapy: Proceedings of the 6th International Congress of Chemotherapy, Volume 1, Baltimore, MD: University Park Press, 718-724.

- Stevens, RM, D Teres, J Skillman, and DS Feingold, 1974, Pneumonia in an Intensive Care Unit: A 30 Month Experience, Arch Intern Med, 134:106-111.

- Teixeira, PJA, R Seligman, FT Hertz, DB Cruz, and JMG Fachel, 2007, Inadequate Treatment of Ventilator-Associated Pneumonia: Risk Factors and Impact on Outcomes, J Hosp Infect, 65:361-367.

- Torres, A, R Aznar, JM Gatell, et al., 1990, Incidence, Risk, and Prognosis Factors of Nosocomial Pneumonia in Mechanically Ventilated Patients, Am Rev Respir Dis, 142:523-528.

The eight studies that evaluated appropriate antibacterial drugs for initial treatment of HABP/VABP (listed in alphabetical order):

- 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.

- Brun-Buisson, C, JP Sollet, S Briere, et al., 1998, Treatment of Ventilator-Associated Pneumonia With Piperacillin-Tazobactam/Amikacin Versus Ceftazidime/Amikacin: A Multicenter, Randomized, Controlled Trial, Clin Infec Dis, 26:346-54.

- 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.

- Joshi, M, M Metzler, M McCarthy, et al., 2006, Comparison of Piperacillin/Tazobactam and Imipenem/Cilastatin, Both in Combination With Tobramycin, Administered Every Six Hours for Treatment of Nosocomial Pneumonia, Respir Med, 100:1554-1565.

- 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.

- Schmitt, DV, E Leitner, T Welte, H Lode, 2006, Piperacillin/Tazobactam Versus Imipenem/Cilastatin in the Treatment of Nosocomial Pneumonia — A Double-Blind, Prospective, Multicenter Study, Infection, 34:127-134.

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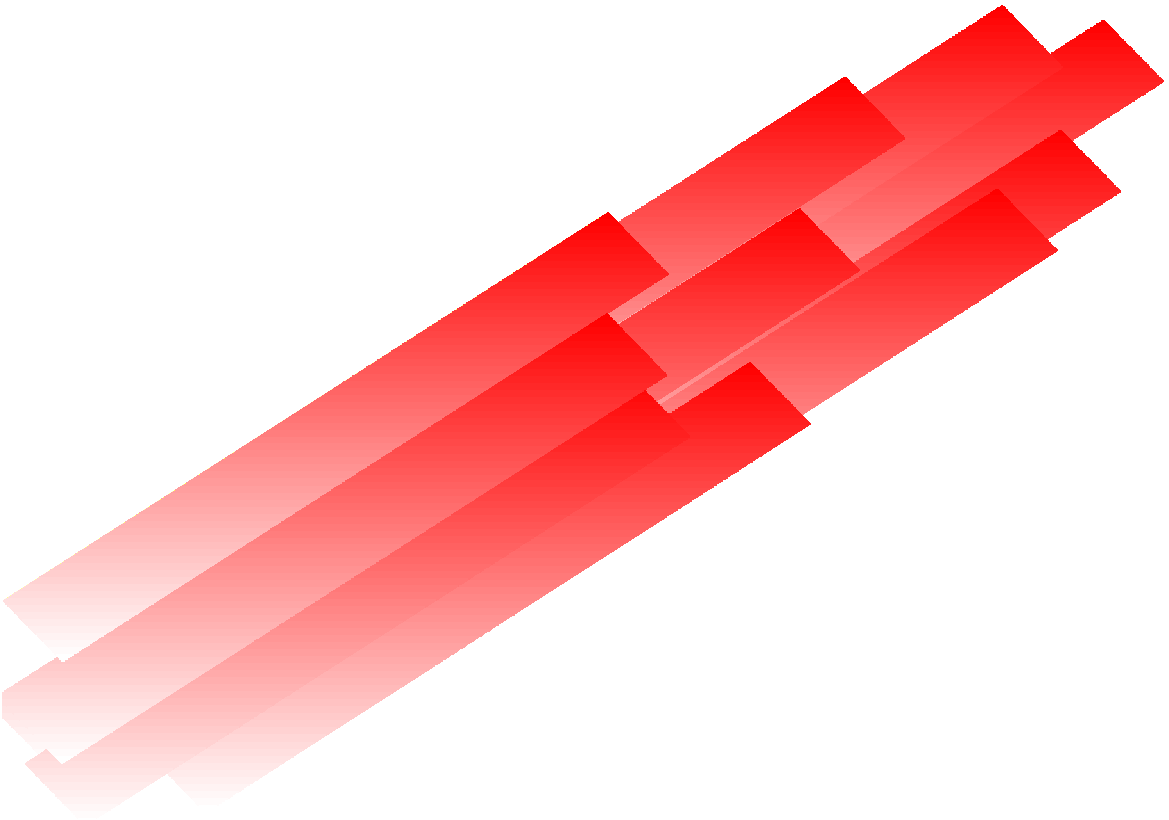
- Wunderink, RG, SK Cammarata, TH Oliphant, et al., 2003, Continuation of a Randomized, Double-Blind, Multicenter Study of Linezolid Versus Vancomycin in the Treatment of Patients With Nosocomial Pneumonia, Clin Ther, 25:980-992.

Guidance for Industry

Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products



U.S. Department of Health and Human Services
Food and Drug Administration
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Guidance for Industry

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TABLE OF CONTENTS

GUIDANCE FOR INDUSTRY[1]

Providing Clinical Evidence of Effectiveness[2] for Human Drug and Biological Products

I. INTRODUCTION

This document is intended to provide guidance to applicants planning to file new drug applications (NDAs), biologics license applications (BLAs), or applications for supplemental indications on the evidence to be provided to demonstrate effectiveness.

This document is also intended to meet the requirements of subsections 403(b)(1) and (2) of the Food and Drug Administration Modernization Act (the Modernization Act) of 1997 for human drug and biological products (P.L. 105-115).[3] Subsection 403(b)(1) directs FDA to provide guidance on the circumstances in which published matter may be the basis for approval of a supplemental application for a new indication. Section III of this guidance satisfies this requirement by describing circumstances in which published matter may partially or entirely support approval of a supplemental application. Subsection 403(b)(2) directs FDA to provide guidance on data requirements that will avoid duplication of previously submitted data by recognizing the availability of data previously submitted in support of an original application to support approval of a supplemental application. Section II of this guidance satisfies this requirement by describing a range of circumstances in which related existing data, whether from an original application or other sources, may be used to support approval of a supplemental application.

In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to add a requirement that, to obtain marketing approval, manufacturers demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies. Since then, the issue of what constitutes sufficient evidence of effectiveness has been debated by the Agency, the scientific community, industry, and others. Sound evidence of effectiveness is a crucial component of the Agency's benefit-risk assessment of a new product or use. At the same time, the demonstration of effectiveness represents a major component of drug development time and cost; the amount

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[1] This guidance document represents the agency's current thinking on providing clinical evidence of effectiveness for human drug and biological products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

[2] As used in this guidance, the term efficacy refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data.

[3] The Modernization Act requirements in Section 403 also apply to animal drugs and medical devices. These products will be addressed in separate guidances.

and nature of the evidence needed can therefore be an important determinant of when and whether new therapies become available to the public. The public health is best served by the development of sound evidence of effectiveness in an efficient manner.

The science and practice of drug development and clinical evaluation have evolved significantly since the effectiveness requirement for drugs was established, and this evolution has implications for the amount and type of data needed to support effectiveness in certain cases. As a result of medical advances in the understanding of pathogenesis and disease staging, it is increasingly likely that clinical studies of drugs will be more narrowly defined to focus, for example, on a more specific disease stage or clinically distinct subpopulation. As a consequence, product indications are often narrower, the universe of possible indications is larger, and data may be available from a number of studies of a drug in closely related indications that bear on a determination of its effectiveness for a new use. Similarly, there may be studies of a drug in different populations, studies of a drug alone or in combination, and studies of different doses and dosage forms, all of which may support a particular new use of a drug. At the same time, progress in clinical evaluation and clinical pharmacology have resulted in more rigorously designed and conducted clinical efficacy trials, which are ordinarily conducted at more than one clinical site. This added rigor and scope has implications for a study's reliability, generalizability, and capacity to substantiate effectiveness.

Given this evolution, the Agency has determined that it would be appropriate to articulate its current thinking concerning the quantitative and qualitative standards for demonstrating effectiveness of drugs and biologics. FDA hopes that this guidance will enable sponsors to plan drug development programs that are sufficient to establish effectiveness without being excessive in scope. The guidance should also bring greater consistency and predictability to FDA's assessment of the clinical trial data needed to support drug effectiveness.

Another major goal of this guidance is to encourage the submission of supplemental applications to add new uses to the labeling of approved drugs. By articulating how it currently views the quantity and quality of evidence necessary to support approval of a new use of a drug, FDA hopes to illustrate that the submission of supplements for new uses need not be unduly burdensome.

II. QUANTITY OF EVIDENCE NECESSARY TO SUPPORT EFFECTIVENESS

A. Legal Standards for Drug and Biological Products

Drugs: The effectiveness requirement for drug approval was added to the Federal Food, Drug, and Cosmetic Act (the Act or the FDC Act) in 1962. Between passage of the Act in 1938 and the 1962 amendments, drug manufacturers were required to show only that their drugs were safe. The original impetus for the effectiveness requirement was Congress's growing concern about the misleading and unsupported claims being made by pharmaceutical companies about their drug products coupled with high drug prices. After two years of hearings on these issues, Congress adopted the 1962 Drug Amendments,

which included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence." *Substantial evidence* was defined in section 505(d) of the Act as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Since the 1962 Amendments added this provision to the statute, discussions have ensued regarding the quantity and quality of the evidence needed to establish effectiveness. With regard to quantity, it has been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness. (See e.g., Final Decision on Benylin, 44 FR 51512, 518 (August 31, 1979); *Warner-Lambert Co. V. Heckler*, 787 F. 2d 147 (3d Cir. 1986)). FDA's position is based on the language in the statute[4] and the legislative history of the 1962 amendments. Language in a Senate report suggested that the phrase "adequate and well-controlled investigations" was designed not only to describe the quality of the required data but the "quantum" of required evidence. (S. Rep. No. 1744, Part 2, 87th Cong. 2d Sess. 6 (1962))

Nevertheless, FDA has been flexible within the limits imposed by the congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing. In some cases, FDA has relied on pertinent information from other adequate and well-controlled studies of a drug, such as studies of other doses and regimens, of other dosage forms, in other stages of disease, in other populations, and of different endpoints, to support a single adequate and well-controlled study demonstrating effectiveness of a new use. In these cases, although there is only one study of the exact new use, there are, in fact, multiple studies supporting the new use, and expert judgment could conclude that the studies together represent substantial evidence of effectiveness. In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval — generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

In section 115(a) of the Modernization Act, Congress amended section 505(d) of the Act to make it clear that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial

[4] Section 505(d) of the Act uses the plural form in defining "substantial evidence" as "adequate and well-controlled investigations, including clinical investigations." See also use of "investigations" in section 505(b) of the Act, which lists the contents of a new drug application.

evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. In making this clarification, Congress confirmed FDA's interpretation of the statutory requirements for approval and acknowledged the Agency's position that there has been substantial progress in the science of drug development resulting in higher quality clinical trial data.

Biologics. Biological products are approved under authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C.§ 262). Under section 351, as in effect since 1944, licenses for biologics have been issued only upon a showing that the products meet standards designed to ensure the "continued safety, purity, and potency" of the products. *Potency* has long been interpreted to include effectiveness (21 CFR 600.3(s)). In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25 (d) (2)). One such adequate alternative was identified to be serological response data where a previously accepted correlation with clinical effectiveness exists. As with nonbiological drug products, FDA has approved biological products based on single, multicenter studies with strong results.

Although section 123(a) of the Modernization Act amended section 351 of the PHS Act to make it clear that separate licenses are not required for biological products and the establishments at which the products are made, the evidentiary standard for a biological product was not changed: the product must be shown to be "safe, pure, and potent" (section 351 (a)(2) of the PHS Act as amended). In the Modernization Act (section 123(f)) Congress also directed the agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved NDAs under section 505(b)(1) of the FDC Act.

B. Scientific Basis for the Legal Standard

The usual requirement for more than one adequate and well-controlled investigation reflects the need for *independent substantiation* of experimental results. A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support for a conclusion of effectiveness. The reasons for this include the following.

- Any clinical trial may be subject to unanticipated, undetected, systematic biases. These biases may operate despite the best intentions of sponsors and investigators, and may lead to flawed conclusions. In addition, some investigators may bring conscious biases to evaluations.

- The inherent variability in biological systems may produce a positive trial result by chance alone. This possibility is acknowledged, and quantified to some extent, in the statistical evaluation of the result of a single efficacy trial. It should be noted, however, that hundreds of randomized clinical efficacy trials are conducted each year with the intent of submitting favorable results to FDA. Even if all drugs tested in such trials were ineffective, one would expect one in forty of those trials to "demonstrate" efficacy by chance alone at conventional levels of statistical significance.[5] It is probable, therefore, that false positive findings (i.e., the chance appearance of efficacy with an ineffective drug) will occur and be submitted to FDA as evidence of effectiveness. Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.

- Results obtained in a single center may be dependent on site or investigator specific factors (e.g., disease definition, concomitant treatment, diet). In such cases, the results, although correct, may not be generalizable to the intended population. This possibility is the primary basis for emphasizing the need for independence in substantiating studies.

- Rarely, favorable efficacy results are the product of scientific fraud.

Although there are statistical, methodologic, and other safeguards to address the identified problems, they are often inadequate to address these problems in a single trial. Independent substantiation of experimental results addresses such problems by providing consistency across more than one study, thus greatly reducing the possibility that a biased, chance, site-specific, or fraudulent result will lead to an erroneous conclusion that a drug is effective.

The need for independent substantiation has often been referred to as the need for replication of the finding. Replication may not be the best term, however, as it may imply that precise repetition of the same experiment in other patients by other investigators is the only means to substantiate a conclusion. Precise replication of a trial is only one of a number of possible means of obtaining independent substantiation of a clinical finding and, at times, can be less than optimal as it could leave the conclusions vulnerable to any systematic biases inherent to the particular study design. Results that are obtained from studies that are of different design and independent in execution, perhaps evaluating different populations, endpoints, or dosage forms, may provide support for a conclusion of effectiveness that is as convincing as, or more convincing than, a repetition of the same study.

[5] p-value = 0.05, two-tailed, which implies an error rate in the efficacy (false positive) tail of 0.025 or one in forty.

C. The Quantity of Evidence to Support Effectiveness

The following three sections provide guidance on the quantity of evidence needed in particular circumstances to establish substantial evidence of effectiveness. Section 1 addresses situations in which effectiveness of a new use may be extrapolated entirely from existing efficacy studies. Section 2 addresses situations in which a single adequate and well-controlled study of a specific new use can be supported by information from other related adequate and well-controlled studies, such as studies in other phases of a disease, in closely related diseases, of other conditions of use (different dose, duration of use, regimen), of different dosage forms, or of different endpoints. Section 3 addresses situations in which a single multicenter study, without supporting information from other adequate and well-controlled studies, may provide evidence that a use is effective.

In each of these situations, it is assumed that any studies relied on to support effectiveness meet the requirements for adequate and well-controlled studies in 21 CFR 314.126. It should also be appreciated that reliance on a single study of a given use, whether alone or with substantiation from related trial data, leaves little room for study imperfections or contradictory (nonsupportive) information. In all cases, it is presumed that the single study has been appropriately designed, that the possibility of bias due to baseline imbalance, unblinding, post-hoc changes in analysis, or other factors is judged to be minimal, and that the results reflect a clear prior hypothesis documented in the protocol. Moreover, a single favorable study among several similar attempts that failed to support a finding of effectiveness would not constitute persuasive support for a product use unless there were a strong argument for discounting the outcomes in the studies that failed to show effectiveness (e.g., study obviously inadequately powered or lack of assay sensitivity as demonstrated in a three-arm study by failure of the study to show efficacy of a known active agent).

Whether to rely on a single study to support an effectiveness determination is not often an issue in contemporary drug development. In most drug development situations, the need to find an appropriate dose, to study patients of greater and lesser complexity or severity of disease, to compare the drug to other therapy, to study an adequate number of patients for safety purposes, and to otherwise know what needs to be known about a drug before it is marketed will result in more than one adequate and well-controlled study upon which to base an effectiveness determination.

This guidance is not intended to provide a complete listing of the circumstances in which existing efficacy data may provide independent substantiation of related claims; rather, it provides examples of the reasoning that may be employed. The examples are applicable whether the claim arises in the original filing of an NDA or BLA, or in a supplemental application.

1. Extrapolation from Existing Studies

In certain cases, effectiveness of an approved drug product for a new indication, or effectiveness of a new product, may be adequately demonstrated without additional adequate and well-controlled clinical efficacy trials. Ordinarily, this will be because other types of data provide a way to apply the known effectiveness to a new population or a different dose, regimen or dosage form. The following are examples of situations in which effectiveness might be extrapolated from efficacy data for another claim or product.

a. Pediatric uses

The rule revising the Pediatric Use section of product labeling (21 CFR 201.57(f)(9)(iv)) makes allowance for inclusion of pediatric use information in labeling without controlled clinical trials of the use in children. In such cases, a sponsor must provide other information to support pediatric use, and the Agency must conclude that the course of the disease and the effects of the drug are sufficiently similar in the pediatric and adult populations to permit extrapolation from adult efficacy data to pediatric patients. Evidence that could support a conclusion of similar disease course and similar drug effect in adult and pediatric populations includes evidence of common pathophysiology and natural history of the disease in the adult and pediatric populations, evidence of common drug metabolism and similar concentration-response relationships in each population, and experience with the drug, or other drugs in its therapeutic class, in the disease or condition or related diseases or conditions. Examples in which pediatric use labeling information has been extrapolated from adult efficacy data include ibuprofen for pain and loratidine for seasonal allergic rhinitis.

b. Bioequivalence

The effectiveness of alternative formulations and new dosage strengths may be assessed on the basis of evidence of bioequivalence.

c. Modified-release dosage forms

In some cases, modified release dosage forms may be approved on the basis of pharmacokinetic data linking the new dosage form to a previously studied immediate-release dosage form. Because the pharmacokinetic patterns of modified-release and immediate-release dosage forms are not identical, it is generally important to have some understanding of the relationship of blood concentration to response, including an understanding of the time course of that relationship, to extrapolate the immediate-release

data to the modified-release dosage form.

d. Different doses, regimens, or dosage forms

Dose-response relationships are generally continuous such that information about the effectiveness of one dose, dosage regimen, or dosage form is relevant to the effectiveness of other doses, regimens, or dosage forms. Where blood levels and exposure are not very different, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data alone. Even if blood levels are quite different, if there is a well-understood relationship between blood concentration and response, including an understanding of the time course of that relationship, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial. In this situation, pharmacokinetic data, together with the well-defined pharmacokinetic/pharmacodynamic (PK/PD) relationship, are used to translate the controlled trial results from one dose, regimen, or dosage form to a new dose, regimen, or dosage form (See also section II.C.2.a).

2. Demonstration of Effectiveness by a Single Study of a New Use, with Independent Substantiation From Related Study Data

The discussion that follows describes specific examples in which a single study of a new use, with independent substantiation from study data in related uses, could provide evidence of effectiveness. In these cases, the study in the new use and the related studies support the conclusion that the drug has the effect it is purported to have. Whether related studies are capable of substantiating a single study of a new use is a matter of judgment and depends on the quality and outcomes of the studies and the degree of relatedness to the new use.

a. Different doses, regimens, or dosage forms

As discussed in Sections II.C.1.d, it may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial where blood levels and exposure are not very different or, even if quite different, there is a well-understood relationship between blood concentration and response. Where the relationship between blood concentration and response is not so well understood and the pharmacokinetics of the new dose, regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness of a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient. For example, a single controlled trial was needed to support the recent approval of a once

daily dose of risperidone because the once daily and twice daily regimens had different pharmacokinetics and risperidone's PK/PD relationship was not well understood.

b. Studies in other phases of the disease

In many cases, therapies that are effective in one phase of a disease are effective in other disease phases, although the magnitude of the benefit and benefit-to-risk relationship may differ in these other phases. For example, if a drug is known to be effective in patients with a refractory stage of a particular cancer, a single adequate and well-controlled study of the drug in an earlier stage of the same tumor will generally be sufficient evidence of effectiveness to support the new use.

c. Studies in other populations

Often, responses in subsets of a particular patient population are qualitatively similar to those in the whole population. In most cases, separate studies of effectiveness in demographic subsets are not needed (see also discussion of the pediatric population in section II.C.1.a) However, where further studies are needed, a single study would ordinarily suffice to support effectiveness in age, race, gender, concomitant disease, or other subsets for a drug already shown to be generally effective in a condition or to be effective in one population. For example, a single study was sufficient to support tamoxifen use in breast cancer in males.

d. Studies in combination or as monotherapy

For a drug known to be effective as monotherapy, a single adequate and well-controlled study is usually sufficient to support effectiveness of the drug when combined with other therapy (as part of a multidrug regimen or in a fixed-dose combination). Similarly, known effectiveness of a drug as part of a combination (i.e., its contribution to the effect of the combination is known) would usually permit reliance on a single study of appropriate design to support its use as monotherapy, or as part of a different combination, for the same use. For example, a single study of a new combination vaccine designed to demonstrate adequate immune response will ordinarily provide sufficient evidence of effectiveness if the new combination contains products or antigens already proven to be effective alone or in other combinations. These situations are common for oncologic and antihypertensive drugs, but occur elsewhere as well.

e. Studies in a closely related disease

Studies in etiologically or pathophysiologically related conditions, or studies of a symptom common to several diseases (e.g., pain) can support each other, allowing initial approval of several uses or allowing additional claims based on a single adequate and well-controlled study. For example, certain anti-coagulant or anti-platelet therapies could be approved for use in two different settings based on individual studies in unstable angina/acute coronary syndrome and in the postangioplasty state. Because the endpoints studied and the theoretical basis for use of an anti-coagulant or anti-platelet drug are similar, each study supports the other for each claim. Similarly, single analgesic studies in several painful conditions would ordinarily be sufficient to support either a general analgesic indication or multiple specific indications. The recent approval of lamotrigine for treatment of Lennox-Gastaut Syndrome (a rare, largely pediatric, generalized seizure disorder) was based on a single adequate and well-controlled trial, due in part to related data showing efficacy of the drug in partial-onset seizures in adults.

f. Studies in less closely related diseases, but where the general purpose of therapy is similar

Certain classes of drug therapy, such as antimicrobials and antineoplastics, are appropriate interventions across a range of different diseases. For therapies of this type, evidence of effectiveness in one disease could provide independent substantiation of effectiveness in a quite different disease. For example, it is possible to argue that evidence of effectiveness of an antimicrobial in one infectious disease setting may support reliance on a single study showing effectiveness in other settings where the causative pathogens, characteristics of the site of infection that affect the disease process (e.g., structure and immunology) and patient population are similar.[6] Similarly, for an oncologic drug, evidence of effectiveness in one or more tumor types may support reliance on a single study showing effectiveness against a different kind of tumor, especially if the tumor types have a common biological origin.

g. Studies of different clinical endpoints

Demonstration of a beneficial effect in different studies on two different clinically meaningful endpoints could cross-substantiate a claim for

[6] See Division of Anti-Infective Drug Products: Points to Consider in the Clinical Development and Labeling of Anti-Infective Drug Products, October 1992.

effectiveness for each outcome. For example, the initial claim for effectiveness of enalapril for heart failure was supported by one study showing symptom improvement over several months and a second study showing improved survival in a more severely ill population. The two different findings, each from an adequate and well-controlled study, led to the conclusion that enalapril was effective in both treating symptoms and improving survival.

h. Pharmacologic/pathophysiologic endpoints

When the pathophysiology of a disease and the mechanism of action of a therapy are very well understood, it may be possible to link specific pharmacologic effects to a strong likelihood of clinical effectiveness. A pharmacologic effect that is accepted as a validated surrogate endpoint can support ordinary approval (e.g., blood pressure effects, cholesterol-lowering effects) and a pharmacologic effect that is considered reasonably likely to predict clinical benefit can support accelerated approval under the conditions described in 21 CFR 314 Subpart H and 21 CFR 601 Subpart E (e.g., CD4 count and viral load effects to support effectiveness of anti-viral drugs for HIV infection). When the pharmacologic effect is not considered an acceptable effectiveness endpoint, but the linkage between it and the clinical outcome is strong, not merely on theoretical grounds but based on prior therapeutic experience or well-understood pathophysiology, a single adequate and well-controlled study showing clinical efficacy can sometimes be substantiated by persuasive data from a well-controlled study or studies showing the related pharmacologic effect.

For example, a single clearly positive trial can be sufficient to support approval of a replacement therapy such as a coagulation factor, when it is combined with clear evidence that the condition being treated is caused by a deficiency of that factor. Demonstration of physical replacement of the deficient factor or restoration of the missing physiologic activity provides strong substantiation of the clinical effect. The corrective treatment of an inborn error of metabolism could be viewed similarly. In the case of preventive vaccines, one adequate and well-controlled clinical trial may be supported by compelling animal challenge/protection models, human serological data, passive antibody data, or pathogenesis information. The more evidence there is linking effects on the pharmacologic endpoint to improvement or prevention of the disease, the more persuasive the argument for reliance on a single clinical efficacy study.

Note, however, that plausible beneficial pharmacologic effects have often not correlated with clinical benefit, and, therefore, caution must be observed in relying on a pharmacologic effect as contributing to evidence

of effectiveness. For example, pharmacologic effects such as arrhythmia suppression by Type 1 antiarrhythmics and increased cardiac output by phosphodiesterase inhibitors or beta adrenergic inotropes resulted in increased mortality, rather than, as was expected, decreased sudden death and improved outcome in heart failure. The reasons for the absence of an expected correlation between pharmacologic and clinical effects are diverse and can include an incompletely understood relationship between the pharmacologic effect and the clinical benefit and the presence of other pharmacologic effects attributable to a drug in addition to the effect being measured and thought to be beneficial. Generally, the utility of pharmacologic outcomes in providing independent substantiation will be greatest where there is prior experience with the pharmacologic class. Even in this case, however, it is difficult to be certain that a pharmacologic effect that correlates with a clinical benefit accounts for all the clinical benefit or that other effects are not present and relevant.

3. Evidence of Effectiveness from a Single Study

When the effectiveness requirement was originally implemented in 1962, the prevailing efficacy study model was a single institution, single investigator, relatively small trial with relatively loose blinding procedures, and little attention to prospective study design and identification of outcomes and analyses. At present, major clinical efficacy studies are typically multicentered, with clear, prospectively determined clinical and statistical analytic criteria. These studies are less vulnerable to certain biases, are often more generalizable, may achieve very convincing statistical results, and can often be evaluated for internal consistency across subgroups, centers, and multiple endpoints.

The added rigor and size of contemporary clinical trials have made it possible to rely, in certain circumstances, on a single adequate and well-controlled study, without independent substantiation from another controlled trial, as a sufficient scientific and legal basis for approval. For example, the approval of timolol for reduction of post-infarction mortality was based on a single, particularly persuasive (low p-value), internally consistent, multicenter study that demonstrated a major effect on mortality and reinfarction rate. For ethical reasons, the study was considered unrepeatable. The Center for Biologics Evaluation and Research has also approved a number of products based upon a single persuasive study. The Agency provided a general statement in 1995 describing when a single, multicenter study may suffice (60 FR 39181; August 1, 1995), but the Agency has not comprehensively described the situations in which a single adequate and well-controlled study might be considered adequate support for an effectiveness claim, or the characteristics of a single study that could make it adequate support for an effectiveness claim.

Whether to rely on a single adequate and well-controlled study is inevitably a matter of judgment. A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study. For this reason, reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. For example, sequential repetition of strongly positive trials that demonstrated a decrease in post-infarction mortality, prevention of osteoporotic fractures, or prevention of pertussis would present significant ethical concerns. Repetition of positive trials showing only symptomatic benefit would generally not present the same ethical concerns.

The discussion that follows identifies the characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim. Although no one of these characteristics is necessarily determinative, the presence of one or more in a study can contribute to a conclusion that the study would be adequate to support an effectiveness claim.

a. Large multicenter study

In a large multicenter study in which (1) no single study site provided an unusually large fraction of the patients and (2) no single investigator or site was disproportionately responsible for the favorable effect seen, the study's internal consistency lessens concerns about lack of generalizability of the finding or an inexplicable result attributable only to the practice of a single investigator. If analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished.

b. Consistency across study subsets

Frequently, large trials have relatively broad entry criteria and the study populations may be diverse with regard to important covariates such as concomitant or prior therapy, disease stage, age, gender or race. Analysis of the results of such trials for consistency across key patient subsets addresses concerns about generalizability of findings to various populations in a manner that may not be possible with smaller trials or trials with more narrow entry criteria. For example, the timolol postinfarction study randomized patients separately within three severity strata. The study showed positive effects on survival in each stratum supporting a conclusion that the drug's utility was not limited to a particular disease stage (e.g., relatively low or high severity).

c. Multiple *studies* in a single study

Properly designed factorial studies may be analyzed as a series of pairwise comparisons, representing, within a single study, separate demonstrations of activity of a drug as monotherapy and in combination with another drug. This model was successfully used in ISIS II, which showed that for patients with a myocardial infarction both aspirin and streptokinase had favorable effects on survival when used alone and when combined (aspirin alone and streptokinase alone were each superior to placebo; aspirin and streptokinase in combination were superior to aspirin alone and to streptokinase alone). This represented two separate (but not completely independent) demonstrations of the effectiveness of aspirin and streptokinase.

d. Multiple endpoints involving different events

In some cases, a single study will include several important, prospectively identified primary or secondary endpoints, each of which represents a beneficial, but different, effect. Where a study shows statistically persuasive evidence of an effect on more than one of such endpoints, the internal weight of evidence of the study is enhanced. For example, the approval of beta-interferon (Betaseron) for prevention of exacerbations in multiple sclerosis was based on a single multicenter study, at least partly because there were both a decreased rate of exacerbations and a decrease in MRI-demonstrated disease activity — two entirely different, but logically related, endpoints.

Similarly, favorable effects on both death and nonfatal myocardial infarctions in a lipid-lowering, postangioplasty, or postinfarction study would, in effect, represent different, but consistent, demonstrations of effectiveness, greatly reducing the possibility that a finding of reduced mortality was a chance occurrence. For example, approval of abciximab as adjunctive treatment for patients undergoing complicated angioplasty or atherectomy was supported by a single study with a strong overall result on the combined endpoint (decreased the combined total of deaths, new infarctions, and need for urgent interventions) and statistically significant effects in separate evaluations of two components of the combined endpoint (decreased new infarctions and decreased need for urgent interventions). In contrast, a beneficial effect on multiple endpoints that evaluate essentially the same phenomenon and correlate strongly, such as mood change on two different depression scales or SGOT and CPK levels postinfarction, does not significantly enhance the internal weight of the evidence from a single trial.

Although two consistent findings within a single study usually provide reassurance that a positive treatment effect is not due to chance, they do not protect against bias in study conduct or biased analyses. For example, a treatment assignment not well balanced for important prognostic variables could lead to an apparent effect on both endpoints. Thus, close scrutiny of study design and conduct are critical to evaluating this type of study.

e. Statistically very persuasive finding

In a multicenter study, a very low p-value indicates that the result is highly inconsistent with the null hypothesis of no treatment effect. In some studies it is possible to detect nominally statistically significant results in data from several centers, but, even where that is not possible, an overall extreme result and significance level means that most study centers had similar findings. For example, the thrombolysis trials of streptokinase (ISIS II, GISSI) had very sizable treatment effects and very low p-values, greatly adding to their persuasiveness. Preventive vaccines for infectious disease indications with a high efficacy rate (e.g., point estimate of efficacy of 80% or higher and a reasonably narrow 95% confidence interval) have been approved based on a single adequate and well-controlled trial.

4. Reliance on a Single, Multicenter Study — Caveats

While acknowledging the persuasiveness of a single, internally consistent, strong multicenter study, it must be appreciated that even a strong result can represent an isolated or biased result, especially if that study is the only study suggesting efficacy among similar studies. Recently, the apparent highly favorable effect of vesnarinone, an inotropic agent, in heart failure (60% reduction of mortality in what appeared to be a well-designed, placebo-controlled, multicenter trial with an extreme p-value) has proven to be unrepeatable. In an attempt to substantiate the finding, the same dose of the drug that seemed lifesaving in the earlier study significantly increased mortality (by 26%), and a lower dose also appeared to have a detrimental effect on survival. Although the population in the second study was, on the whole, a sicker population than in the first, the outcomes in similarly sick patients in each study were inconsistent so this factor does not explain the contradictory results.

When considering whether to rely on a single multicenter trial, it is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single multicenter trial. In the case of vesnarinone, there were other data that were not consistent with the dramatically favorable outcome in the multicenter study. These data seemed to show an inverse dose-response relationship, showed no suggestion

of symptomatic benefit, and showed no effect on hemodynamic endpoints. These inconsistencies led the Agency, with the advice of its Cardio-Renal Advisory Committee, to refuse approval — a decision borne out by the results of the subsequent study.

This example illustrates how inadequacies and inconsistencies in the data, such as lack of pharmacologic rationale and lack of expected other effects accompanying a critical outcome, can weaken the persuasiveness of a single trial. Although an unexplained failure to substantiate the results of a favorable study in a second controlled trial is not proof that the favorable study was in error — studies of effective agents can fail to show efficacy for a variety of reasons — it is often reason not to rely on the single favorable study.

III. DOCUMENTATION OF THE QUALITY OF EVIDENCE SUPPORTING AN EFFECTIVENESS CLAIM

When submitting the requisite quantity of data to support approval of a new product or new use of an approved product, sponsors must also document that the studies were adequately designed and conducted. Essential characteristics of adequate and well-controlled trials are described in 21 CFR 314.126. To demonstrate that a trial supporting an effectiveness claim is adequate and well-controlled, extensive documentation of trial planning, protocols, conduct, and data handling is usually submitted to the Agency, and detailed patient records are made available at the clinical sites.

From a scientific standpoint, however, it is recognized that the extent of documentation necessary depends on the particular study, the types of data involved, and the other evidence available to support the claim. Therefore, the Agency is able to accept different levels of documentation of data quality, as long as the adequacy of the scientific evidence can be assured. This section discusses the factors that influence the extent of documentation needed, with particular emphasis on studies evaluating new uses of approved drugs.

For the purposes of this section, the phrase *documentation of the quality of evidence* refers to (1) the completeness of the documentation and (2) the ability to access the primary study data and the original study-related records (e.g., subjects' medical records, drug accountability records) for the purposes of verifying the data submitted as evidence. These interrelated elements bear on a determination of whether a study is adequate and well-controlled.

In practice, to achieve a high level of documentation, studies supporting claims are ordinarily conducted in accordance with good clinical practices (GCPs). Sponsors routinely monitor all clinical sites, and FDA routinely has access to the original clinical protocols, primary data, clinical site source documents for on-site audits, and complete study reports.

However, situations often arise in which studies that evaluate the efficacy of a drug product lack the full documentation described above (for example, full patient records may not be available) or in which the study was conducted with less monitoring than is ordinarily seen in commercially sponsored trials. Such situations are more common for supplemental indications because postapproval studies are more likely to be conducted by parties other than the drug sponsor and those parties may employ less extensive monitoring and data-gathering procedures than a sponsor. Under certain circumstances, it is possible for sponsors to rely on such studies to support effectiveness claims, despite less than usual documentation or monitoring. Some of those circumstances are described below.

A. Reliance on Less Than Usual Access to Clinical Data or Detailed Study Reports

FDA's access to primary data has proven to be important in many regulatory decisions. There are also reasons to be skeptical of the conclusions of published reports of studies. Experience has shown that such study reports do not always contain a complete, or entirely accurate, representation of study plans, conduct and outcomes. Outright fraud (i.e., deliberate deception) is unusual. However, incompleteness, lack of clarity, unmentioned deviation from prospectively planned analyses, or an inadequate description of how critical endpoint judgments or assessments were made are common flaws. Typically, journal article peer reviewers only have access to a limited data set and analyses, do not see the original protocol and amendments, may not know what happened to study subjects that investigators determined to be non-evaluable, and thus may lack sufficient information to detect critical omissions and problems. The utility of peer review can also be affected by variability in the relevant experience and expertise of peer reviewers. FDA's experiences with the Anturane Reinfarction Trial, as well as literature reports of the efficacy of tacrine and the anti-sepsis HA-1A antibody, illustrate its concerns with reliance on the published medical literature.

Notwithstanding these concerns, the presence of some of the factors discussed below can make it possible for FDA to rely on studies for which it has less than usual access to data or detailed study reports to partially or entirely (the so-called *paper* filing) support an effectiveness claim. FDA's reliance on a literature report to support an effectiveness claim is more likely if FDA can obtain additional critical study details. Section 1 below describes additional information that, if available, would increase the likelihood that a study could be relied on to support an effectiveness claim. Section 2 describes factors that may make efficacy findings sufficiently persuasive to permit reliance on the published literature alone. Note that the factors outlined in Section 2 are relevant to an assessment of the reliability of literature reports generally, whether alone, or accompanied by other important information as discussed in Section 1.

1. Submission of Published Literature or Other Reports in Conjunction with Other Important Information that Enhances the Reliability of the Data

If a sponsor wishes to rely on a study conducted by another party and cannot obtain the primary data from the study, for most well-conducted studies it is possible to obtain other important information, such as a protocol documenting the prospective plans for the trial, records of trial conduct and procedures, patient data listings for important variables, and documentation of the statistical analysis. FDA has considerable experience evaluating large multicenter outcome studies sponsored by U.S. and European government agencies (NIH, British Medical Research Council) and private organizations (the ISIS studies, the SAVE study) for which there was limited access to primary study data, but for which other critical information was available. Providing as many as possible of the following important pieces of information about a study, in conjunction with the published report, can increase the likelihood that the study can be relied on to support an effectiveness claim:

a. The protocol used for the study, as well as any important protocol amendments that were implemented during the study and their relation to study accrual or randomization.

b. The prospective statistical analysis plan and any changes from the original plan that occurred during or after the study, with particular note of which analyses were performed pre- and post-unblinding.

c. Randomization codes and documented study entry dates for the subjects.

d. Full accounting of all study subjects, including identification of any subjects with on-treatment data who have been omitted from analysis and the reasons for omissions, and an analysis of results using all subjects with on-study data.

e. Electronic or paper record of each subject's data for critical variables and pertinent baseline characteristics. Where individual subject responses are a critical variable (e.g., objective responses in cancer patients, clinical cures and microbial eradications in infectious disease patients, death from a particular cause), detailed bases for the assessment, such as the case report, hospital records, and narratives, should be provided when possible.

f. Where safety is a major issue, complete information for all deaths and drop-outs due to toxicity. For postapproval supplemental uses, however, there is generally less need for the results of lab tests or for details of adverse event reports and, consequently, much more limited documentation may be sufficient (e.g., only for unexpected deaths and previously undescribed serious adverse effects). Exceptions to this

approach would include situations in which the population for the supplemental use is so different that existing safety information has limited application (e.g., thrombolysis in stroke patients versus myocardial infarction patients) or where the new population presents serious safety concerns (e.g., extension of a preventive vaccine indication from young children to infants).

2. Submission of Published Literature Reports Alone

The following factors increase the possibility of reliance on published reports alone to support approval of a new product or new use:

a. Multiple studies conducted by different investigators where each of the studies clearly has an adequate design and where the findings across studies are consistent.

b. A high level of detail in the published reports, including clear and adequate descriptions of statistical plans, analytic methods (prospectively determined), and study endpoints, and a full accounting of all enrolled patients.

c. Clearly appropriate endpoints that can be objectively assessed and are not dependent on investigator judgment (e.g., overall mortality, blood pressure, or microbial eradication). Such endpoints are more readily interpreted than more subjective endpoints such as cause-specific mortality or relief of symptoms.

d. Robust results achieved by protocol-specified analyses that yield a consistent conclusion of efficacy and do not require selected post hoc analyses such as covariate adjustment, subsetting, or reduced data sets (e.g., analysis of only responders or compliant patients, or of an "eligible" or “evaluable” subset).

e. Conduct of studies by groups with properly documented operating procedures and a history of implementing such procedures effectively.

There have been approvals based primarily or exclusively on published reports. Examples include the initial approval of secretin for evaluation of pancreatic function and recent approvals of bleomycin and talc for malignant pleural effusion and doxycycline for malaria.

B. Reliance on Studies with Alternative, Less Intensive Quality Control/On-Site Monitoring

Industry-sponsored studies typically use extensive on-site and central monitoring and auditing procedures to assure data quality. Studies supported by other sponsors may employ less stringent procedures and may use no on-site monitoring at all. An International Conference on Harmonisation guideline on good clinical practices,[7] recently accepted internationally, emphasizes that the extent of monitoring in a trial should be based on trial-specific factors (e.g., design, complexity, size, and type of study outcome measures) and that different degrees of on-site monitoring can be appropriate. In recent years, many credible and valuable studies conducted by government or independent study groups, often with important mortality outcomes, had very little on-site monitoring. These studies have addressed quality control in other ways, such as by close control and review of documentation and extensive guidance and planning efforts with investigators. There is a long history of reliance on such studies for initial approval of drugs as well as for additional indications. Factors that influence whether studies with limited or no monitoring may be relied on include the following:

1. The existence of a prospective plan to assure data quality.

2. Studies that have features that make them inherently less susceptible to bias, such as those with relatively simple procedures, noncritical entry criteria, and readily assessed outcomes.

3. The ability to sample critical data and make comparisons to supporting records (e.g., hospital records).

4. Conduct of the study by a group with established operating procedures and a history of implementing such procedures effectively.

[7] International Conference on Harmonisation Guidance for Industry E6, *Good Clinical Practice: Consolidated Guideline*, April 1996.

Comments Submitted to Docket No. FDA-2010-D-0589 regarding the draft guidance entitled, "Guidance for Industry, Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment", dated November 2010.

AdvanDx

Division of Dockets Management (HFA-305)
FDA
5630 Fisher Lane, rm 1061
Rockville, MD 20852

Submitted electronically at http://www.regulations.gov.

RE: Docket No. FDA-2010-D-0589
Draft Guidance for Industry: Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment

To whom it may concern,

AdvanDx would like to offer comment regarding the above referenced guidance document concerning studies in the development of Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP) treatments. AdvanDx is a small developer and manufacturer of advanced molecular *in vitro* diagnostic devices.

We have read with interest section III (A) 3 which emphasizes the importance of having bacteriological confirmation of the etiology of HABP and VABP in study populations of new therapies for these disease entities. A current dilemma for patient recruitment in these types of trials is that the infectious agent is not known at the time the patient is enrolled since conventional microbiological identification methods (of specimens from the lower respiratory tract) may take greater than 24 hours. This delayed knowledge may result in study medication being administered to ineligible subjects or other inappropriate patient/subject management. In section III (B) 3, line 359-362, it is mentioned that “the use of rapid diagnostic tests for bacterial pathogens…” should be discussed with FDA prior to initiation of a clinical trial which would seem to begin to address this issue. Given the importance of identification of the causative agent as an inclusion criterion for these studies we believe it would be appropriate for FDA to strengthen this statement.

The technology for development of rapid diagnostics assays currently exist for HAPB and VABP associated pathogens (e.g. Gram-negative organisms). It has been our experience in discussions with pharmaceutical companies that they recognize rapid pathogen identification as being beneficial to patient enrollment for clinical trials. However, they are concerned that if a rapid diagnostic test is used to enroll patients in a study for a new compound then FDA will require the use of that test or a similar assay as a set condition (label requirement) for eventual prescribing of the compound. The negative impact on potential marketing of a compound due to a labeling requirement for the use of a particular diagnostic test currently outweighs, in their opinion, the

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positive benefits of using rapid diagnostics to enroll and stratify patients during clinical trials and/or enlisting IVD companies to develop such therapy-specific assays.

Similarly, while diagnostic companies, such as AdvanDx, appreciate the benefit of using rapid diagnostics for clinical trials of HAPB/VABP therapies, they lack financial incentive to develop such assays since financial opportunities would be of limited size and duration unless the assays could be more broadly indicated beyond the clinical studies.

In summary, we believe that FDA should clarify its position on the use of rapid diagnostics for clinical trials of HABP/VABP therapies by clearly communicating the impact of such use on pharmaceutical labeling. Additionally, FDA should offer an accelerated clearance process for rapid IVDs that are to be associated with clinical trials of new drug compounds for HABP/VABP. Such a process should take into account the need of clinical trials to improve the speed, efficiency, and quality of data generated during the studies of new HABP/VABP treatments.

Thank you for the opportunity to comment on this matter.

H. Stender
VP Research and Development

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February 20, 2011

Joseph Toerner, MD, MPH
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Dear Dr. Toerner:

The Society of Critical Care Medicine (SCCM) is pleased to provide comment on the draft guidance entitled ***Guidance for Industry: Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment***, which was published for public comment in the Federal Register in November, 2010.

The Society is the largest multiprofessional organization dedicated to ensuring excellence and consistency in the practice of critical care. With more than 15,000 members in more than 100 countries, SCCM is the only organization that represents all professional components of the critical care team. The mission of SCCM is to secure the highest quality care for all critically ill and injured patients.

The draft guidance was reviewed by a cross-section of the SCCM membership intimately familiar with the clinical problems [hospital-acquired (HABP) or ventilator-associated bacterial pneumonia (VABP)] addressed by the guidance.
On the whole, the guidance is a well-written, scholarly document that includes the necessary details and definitions.

We have identified a number of areas where further clarification is desirable. In addition, current clinical practice has progressed significantly since many of the studies cited were carried out, and thus the guidance should either include or specifically address some of these changes. Specific questions, comments, and/or suggestions follow:

1. Consider clarification regarding definitions of HABP and VABP, including the methods used for radiographic, clinical, and microbiologic diagnosis.
    a. For radiographic confirmation of a new infiltrate, consider clarification that the infiltrate should be new and not attributable to other causes such as position, atelectasis, or fluid. In addition, computed tomography and magnetic resonance imaging are being applied more frequently and may provide more specific information than plain chest radiographs. While neither should be required, they may identify new infiltrates not appreciated with routine chest radiographs.
    b. Egophony cannot be used as part of the clinical auscultatory diagnosis of VABP since the intubated patient cannot phonate.

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c. Although appropriate lower respiratory tract specimens are required for microbiologic identification in the draft guidance, they are not used for VAPB diagnosis. Consider quantitative lower respiratory tract cultures [bronchoalveolar lavage (BAL) or mini-BAL with $>10^4$ organisms on quantitative culture] for VAPB diagnosis. This provides a clear microbiologic diagnosis of VAPB and is now commonly used in critical care nationwide.[1]
d. Consider inclusion of additional, evolving microbiologic pathogen identification assays (e.g., fluorescence in situ hybridization, polymerase chain reaction, peptide nucleic acid probes) and other emerging technologies that aid in rapid pathogen identification.

2. The guidance currently states, "In addition, patients with VABP should have a Clinical Pulmonary Infection Score of greater than 6 and at least one of the following present at enrollment:
   a. Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (e.g., dullness on percussion, bronchial breath sounds or egophony)
   b. Acute changes made in the ventilator support system to enhance oxygenation, as determined by arterial blood gas, or worsening PaO_2/FiO_2."

   There is significant concern that the Clinical Pulmonary Infection Score (CPIS) is not valid in the diagnosis of ventilator-associated pneumonia (VAP). A recent study by the Canadian Critical Care Trials Group examined 740 patients enrolled in a multicenter randomized trial and assessed the value of CPIS to diagnose VAP. The receiver operating characteristic for the area under the curve (ROC AUC) for CPIS was not significant (0.47; 95% confidence interval, 0.42-0.53), meaning that no threshold was clinically useful. The CPIS was of limited use in the diagnosis of VAP in this and many other studies, particularly in surgical, trauma, and burn patients, and should not be used to aid diagnosis or as a risk stratification tool in HABP/VABP studies. This is particularly relevant, as the highest rates of VAP are currently in the surgical, trauma, and burn intensive care units (ICUs).

   The requirement of "2a" or "2b" as necessary for VABP diagnosis is of significant concern. Abnormal pulmonary examination findings are very common in all mechanically ventilated ICU patients, and most are due to atelectasis and edema, not pneumonia, particularly in our current era of aggressive VAP prevention. Furthermore, changes in oxygenation in a mechanically ventilated patient are more commonly related to the ventilator strategies employed, particularly the degree of positive end-expiratory pressure and mean airway pressure, and less commonly related to pneumonia.[2, 3]

3. It would be helpful to include a table summarizing the definition (clinical, radiographic, and microbiologic) for HABP and VABP, since the two terms sometimes are used interchangeably throughout the guidance. A table would make clear the necessary attributes, exclusions, and cutoff criteria for each condition.

4. Concerns persist within the critical care community regarding the emphasis on 28-day mortality as the primary endpoint. The guidance states "Currently, we do not recognize any surrogate markers or clinical endpoints as substitutes for all-cause mortality in HABP/VABP trials." Furthermore, within the present guidance, patients for inclusion in Phase III trials should be identified with a 20% mortality endpoint (with treatment) as the goal. Great efforts have been ongoing with respect to HABP and VABP to impact the incidence and mortality, to the extent that mortality – particularly a 20% mortality – may no longer be a useful goal.
   a. The recent study by Chastre et al[4] enrolled 531 patients and was the largest clinical trial ever conducted of an investigational drug for VAP. The authors reported the all-cause mortality at day 28 was 10.8% with doripenem and 9.5% with imipenem. This mortality rate is much lower than in prior studies, but is representative of current VAP mortality rates in our ICUs. If enrollment of more unstable patients with septic shock, acute respiratory distress syndrome (ARDS) or multiple organ failure (MOF) is desired in VAPB clinical trials, there is significant concern that the mortality rate will reflect the clinical and critical care management of these

diseases (septic shock, ARDS, MOF), and will not reflect the efficacy of the antimicrobials being studied.

5. The current guidance states as an Exclusion Criteria: "Patients who have received prior antibacterial drugs within the past 30 days with activity against bacterial pathogens that cause HABP/VABP."
    a. This will negatively impact the ability to enroll surgical and trauma patients in these clinical trials and, as stated previously, these are the patients with the highest VAPB rates at present in the United States.
    b. Surgical and trauma patients commonly receive a single dose of antimicrobials preoperatively or a short course of antimicrobials for another infectious etiology. Exclusion of these patients will significantly impair study enrollment.

SCCM appreciates the opportunity to provide commentary on the FDA HABP/VABP draft guidance in an effort to advance the development of new and improved antibacterial therapies to treat HABP and VABP.

Respectfully submitted,

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February 20, 2011

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The Surgical Infection Society (SIS) writes to comment on the draft guidance entitled *Guidance for Industry: Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment*, published for public comment in the Federal Register in November, 2010.

The mission of the SIS is to educate health care providers and the public about infection in surgical patients and promote research in the understanding, prevention, and management of surgical infections. The SIS is comprised of clinician-scientists who provide intensive care to critically ill or –injured surgical and trauma patients, who comprise currently the highest-risk groups of patients for development of hospital-acquired (HABP) or ventilator-associated bacterial pneumonia (VABP) according to data of the National Healthcare Safety Network of the U.S. Centers for Disease Control and Prevention [1]. Members of SIS belong also to virtually every regional and national surgical society in the United States. Our members perform basic and applied research in injury and inflammation biology, host defenses, and pathogenesis of infection, and clinical trials of prevention and treatment of infections that surgical patients develop, either as primary disease or complications of treatment. As critical care surgeons, members of SIS manage patients with HABP/VABP regularly, enroll such patients in clinical trials, and often serve as site principal investigators for such trials. Members of SIS participated as co-moderators and presenters for the Workshop held in Bethesda, MD in 2009, published recently in *Clinical Infectious Diseases* [2]. Moreover, the SIS publishes clinical practice guidelines for the management of complicated infections [3,4] for the benefit of the medical profession, and thus is informed regarding clinical trial design and the evaluation and grading of evidence. Finally, the SIS, via its Foundation, supports the training of promising future investigators in relevant areas through the competitive awarding of mentored starter grants in both basic and clinical research. Therefore, it should be clear that SIS is a major stakeholder in this discussion.

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For several reasons the draft guidance, in the opinion of SIS, will make it almost impossible to perform a clinical trial for HABP/VAPB, at least in surgical patients, who as noted now constitute the major reservoir of potential enrollees.

1. The only primary endpoint that is recognized is mortality, and patients enrolled would have to have an expected 20% mortality. Given this target population, most patients would have to have severe sepsis, if not septic shock, as a result of the HABP/VAPB, to account for the degree of mortality anticipated and expected. By definition, patients with severe sepsis have organ dysfunction [5,6], and it is known that most patients who succumb with respiratory failure do so not because of an inability to oxygenate or ventilate, but rather because of the magnitude of non-pulmonary organ dysfunction they manifest [7,8]. It is certain that many potential enrollees would have to be excluded from a study for some extra-pulmonary manifestation of the multiple organ dysfunction syndrome (e.g., renal or hepatic dysfunction, thrombocytopenia).
2. There seems to be little role, if any, in the draft guidance for other clinical endpoints, despite detailed discussion at the Workshop, and it appears as if those would have to include some sort of "patient-reported outcome". This is unrealistic, considering that these patients are likely to be critically ill and that a substantial proportion of the patients (those who die) may never recover to the point where they become valid observers/reporters. The issue of endpoints deserves substantial reconsideration.
3. Patients will be excluded who have received any antibiotic potentially effective for HABP/VABP anytime in the previous 30 days. This criterion alone will make it nearly impossible to enroll surgical patients, the majority of whom will have received antibiotic therapy for the infections that made them critically ill to begin with (e.g., complicated intra-abdominal infection). Numerous antibiotics are indicated for both complicated intra-abdominal infections and nosocomial pneumonia (e.g., ciprofloxacin, meropenem, piperacillin/tazobactam), and these antibiotics are preferred for high-risk patients, according to current guidelines [3]. Consider the example of a high-risk patient who is critically ill after surgery for a colon anastomotic dehiscence in the post-operative period, who received cefoxitin prophylaxis for the elective colon resection and was treated appropriately for the complication of peritonitis with reoperation and piperacillin/tazobactam. This patient, at high risk for pneumonia due to prolonged mechanical ventilation and at high risk of death should VAP ensue [9], would be excluded (inappropriately, in our view) from trials going forward. Moreover, it is difficult to imagine a seriously- or critically ill surgical patient who has not received some sort of antibiotic in the previous 30 days. It is unclear how a potentially effective antibiotic would be defined; would prophylactic cefazolin for a hip operation cause a patient to be excluded because the drug is potentially effective against some strains of common pathogens such as *E. coli* and *Klebsiella* spp.?
4. The SIS disagrees with the draft guidance regarding use of clinical severity scoring systems in several respects:

a. Organ failure/dysfunction scores describe outcomes [10], not inclusion criteria, and should not be used to describe the comparability of enrolled groups, unless resolution of organ dysfunction is an objective, recognized endpoint for a study, in which case the chosen score should be calculated serially during the study period.
b. The Predisposition, Insult, Response, and Organ Dysfunction Score (PIRO) is purely descriptive and neither quantifiable, nor validated for this purpose. Its use cannot be recommended.
c. The Clinical Pulmonary Infection Score (CPIS) has been discredited for use with surgical patients, as was made clear in the workshop proceedings [11]. Considering that surgical patients are the main reservoir of potential enrollees, CPIS cannot be recommended or relied upon.

The SIS appreciates the opportunity to provide commentary, and looks forward to partnering with FDA and industry sponsors to ensure optimal design and conduct of clinical trials of anti-infective therapy for HABP/VABP.

Sincerely yours,

Henri R. Ford

Henri R. Ford, MD, MHA
President

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February 28, 2011

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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment
(Docket No. FDA-2010-D-0589)

Dear Sir or Madam:

Cubist is a biopharmaceutical company focused on the research, development and commercialization of pharmaceutical products – especially antibiotics -- that address unmet medical needs in the acute care environment. Headquartered in Lexington, Massachusetts, we currently market CUBICIN® (daptomycin for injection), the first intravenous (IV) antibiotic from a class of anti-infectives called lipopeptides. CUBICIN received FDA approval in 2003 for the treatment of complicated skin and skin structure infections caused by certain susceptible strains of Gram-positive microorganisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). CUBICIN is also approved in the U.S. for the treatment of *S. aureus* bloodstream infections (bacteremia), and is the only IV antibiotic approved for this indication based on the results of a prospective, randomized, controlled registration trial. In the wake of a highly successful launch of CUBICIN, the company has a growing pipeline that includes antibiotic candidates for difficult to treat infections including *Clostridium difficile* and serious Gram-negative infections, including those caused by multi-drug resistant *Pseudomonas aeruginosa.*

Cubist welcomes the opportunity to comment on this draft guidance. For clarity, the text of the draft guidance is in bold, Cubist's responses are in plain text.

Lines 105-119: **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.**
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. Although some epidemiological studies have shown that patients with VABP may be more likely to have bacterial pathogens resistant to multiple antibacterial drugs, these pathogens have also been observed in HABP and therefore the guidance considers these two clinical disease entities together, referred to as HABP/VABP.

FDA-2010-D-0589

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Cubist comment: As patients in these clinical trials will be ventilated in the hospital setting, patients meeting the minimum required duration of ventilation for VABP will also have met the minimum duration of hospital stay required for a diagnosis of HABP, as defined in the draft document. Thus, VABP appears to be a subset of HABP with the added criteria of receipt of mechanical ventilation. However, further in the document, the two patient populations are discussed as being mutually exclusive, i.e. HABP is equivalent to non-VABP.

Suggested action: Clarify whether HABP and VABP are two distinct patient populations, or if one is largely a subset of the other.

Lines 121-125: **The more general term *health care-associated pneumonia*, or pneumonia among persons residing in chronic care facilities such as nursing homes, is not considered to be HABP as defined in this guidance because the bacterial pathogens in these patients with the broader category of health-care associated pneumonia are, in general, less likely to be similar to bacterial pathogens in patients with HABP/VABP.**

Cubist comment: The 2005 clinical guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia (HCAP) from the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) include HCAP in the spectrum of HABP and VABP and recommend that patients with HCAP receive therapy for multi-drug resistant (MDR) pathogens. This recommendation is based on the similarity between the etiology of HCAP and HABP/VABP that commonly includes aerobic Gram-negative bacilli, such as *P. aeruginosa*, *E. coli*, *K. pneumoniae*, and *Acinetobacter* species as well as Gram-positive cocci, such as methicillin-resistant *S. aureus* (MRSA).

The draft guidance cites two epidemiological studies to support the conclusion that the microbial etiology of the two patient populations is different. Specifically, reference is made to a lower prevalence of *P. aeruginosa* in HCAP vs. HABP/VABP (4-14% vs. 25%, respectively). Of note, the incidence of MRSA and *S. pneumoniae* in HCAP in these same papers was 23 - 33% and 5-9%, respectively, consistent with the reported incidence of MRSA and *S. pneumoniae* in HABP/VABP.

Further evidence that HCAP, as defined in the 2005 ATS/IDSA guidelines, has an etiology similar to HABP/VABP is provided in a study by Kollef *et al.* showing the microbiology and outcomes of 4,543 patients with culture-positive community-acquired pneumonia (CAP), HCAP, HABP, and VABP. The frequency of isolation of different bacterial pathogens in each pneumonia population is summarized in the table below:

Pathogen	**CAP (n=2221)**	**HCAP (n=988)**	**HABP (n=835)**	**VABP (n=499)**
S. aureus	25.5%	46.7%	47.1%	42.5%
MRSA	6.2%	18.3%	16.8%	11.8%
Pseudomonas sp.	17.1%	25.3%	18.4%	21.1%
Klebsiella sp.	9.5%	7.6%	7.1%	8.4%
E. coli	4.8%	5.2%	4.7%	6.4%
Acinetobacter sp.	1.6%	2.6%	2.0%	3.0%
S. pneumoniae	16.6%	5.5%	3.1%	5.8%
Mortality				
	10.0%	19.8%	18.8%	29.3%

The table shows that the implicated bacterial pathogens are isolated at similar frequency in HCAP, HABP, and VABP. Interestingly, in this study *P. aeruginosa* was isolated more frequently in patients with HCAP compared to HABP or VABP and the incidence of *S. pneumoniae* was substantially less in HCAP compared to CAP. There was no significant difference in mean mortality rates between HCAP and HAP ($p > 0.05$). In contrast, the relatively high incidence of *S. pneumoniae,* low incidence of *S. aureus,* and low mortality rate in CAP serve to distinguish it from the other types of pneumonia.

In addition, Schreiber *et al.* provide supplementary evidence that patients with HCAP are more likely to be infected with resistant organisms, closely resembling the risk faced by patients with HABP. The table below shows that the HCAP can be distinguished from CAP in terms of the frequency of isolation of resistant pathogens with significant differences seen for *P. aeruginosa* and extended spectrum beta-lactamases (ESBLs). As it is likely that target pathogens for new drugs being evaluated in HABP will include MRSA or resistant gram negative bacteria, the potential for resistant pathogens in the HCAP population makes this population suitable for inclusion in HABP trials.

Pathogen	CAP	HCAP	P Value
MRSA	14.6%	22.3%	P=0.193
P. aeruginosa	3.1%	23.4%	P=0.001
ESBLs	0	2.1%	P=0.001

In summary, the data indicate that HCAP is distinct from CAP and closely resembles HABP with respect to etiology (including MDR pathogens) and mortality.

Suggested action: Include HCAP patients in studies of HABP and VABP (if mechanically ventilated), as these patients are a source of difficult-to-treat pathogens and, therefore, an important target for new drugs that could treat such pathogens.

***Lines 208-209*: All adverse events should be followed until resolution, even if time on trial would otherwise have been completed.**

Cubist comment: Although appropriate for serious adverse events to be followed through resolution, we are unaware of any other safety guidelines that recommend following all adverse events through resolution. Most intravenous antibiotics administered in the hospital setting have a relatively short half-life and are administered for 10 days or less. Additionally, a large number of adverse events are typically reported in these trials (77% of the population in the doripenem nosocomial pneumonia study [Rea-Neto], and 82% of the population in the telavancin HABP studies [Rubinstein]). Consequently, following all events through resolution is not likely to provide greater insight into the causality or relatedness of the event to the antibiotic than following them until the end of the study, nor provide additional information for inclusion in the label that would be useful to clinicians.

Suggested action: Follow only serious adverse events through resolution. Non-serious adverse events should be followed through study completion.

Lines 214-216: **Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data.**

Cubist comment: Although agreed that age- and sex-appropriate normal values should be included when reporting laboratory data, it is unclear what is meant by the additional statement: "with clinical measurements."

Suggested action: Clarify what is meant by the above statement.

Lines 259-273: **Clinical criteria. Patients should have the following clinical findings that support a diagnosis of HABP/VABP:**

- **Documented fever, defined as an oral or tympanic temperature greater than or equal to 38 degrees Celsius (100.4 degrees Fahrenheit), or a core temperature greater than or equal to 38.3 degrees Celsius (101 degrees Fahrenheit) or hypothermia, defined as a core body temperature of less than 35 degrees Celsius (95.2 degrees Fahrenheit); axillary temperatures are not recommended**
- **An elevated total peripheral white blood cell (WBC) count (WBC greater than 269 10,000/mm); or greater than 15 percent immature neutrophils (bands), regardless of total peripheral WBC count; or leukopenia with total WBC less than 4,500/mm**
- **New onset of expectorated or suctioned respiratory secretions characterized by purulent appearance indicative of bacterial pneumonia**

Cubist comment: The 2005 ATS/IDSA clinical guidelines reference a study by Fabergas *et al.* and state, "The presence of a new or progressive radiographic infiltrate plus at least two of three clinical features... represents the most accurate combination of criteria for starting empiric antibiotic therapy." The table below summarizes the findings from the study:

Variables	Sensitivity % (n)	Specificity % (n)	PPV % (n)	NPV % (n)
Chest radiograph + 2 of 3 clinical criteria*	69 (9/13)	75 (9/12)	75 (9/12)	69 (9/13)
Chest radiograph + all 3 clinical criteria*	23 (3/13)	92 (11/12)	75 (3/4)	52 (11/21)

*Clinical criteria: leukocytosis, fever, purulent secretions

The use of all three clinical criteria, in addition to a chest radiograph, provided the highest specificity but at a large cost to sensitivity. Data were generated from post-mortem patients suggesting that all of these patients would have been sufficiently ill for enrollment into HABP/VABP trials as proposed in the draft guidance (i.e. with a all cause mortality >20%); however, it should be noted that only 3 of 13 patients had all three clinical criteria in addition to a chest radiograph suggestive of pneumonia. Thus, despite the high specificity of the diagnosis when all three clinical criteria are required for entry, a large proportion of patients with a diagnosis of nosocomial pneumonia would be excluded. As a result, the population as defined in the draft guidance would not be representative of the larger population suitable for treatment with the study drug in clinical practice.

Patients at risk for nosocomial pneumonia frequently do not manifest all three clinical criteria because the physiologic response to infection is diminished in certain patient subpopulations.

Supporting evidence is provided in a study by Finkelstein *et al.* that compared the responses of older (65+ years of age) and younger (20-49 years of age) adults to an acute bacterial infection, more specifically *S. pneumoniae* bacteremia. Temperature on admission, number of patients with temperature < 100°F, and peak temperature while hospitalized were all significantly higher in younger adults than older adults [102.5°F ± 2.4 vs. 100.8°F ± 2.5; 8 (9%) vs. 16 (29%); and 103.5°F ± 1.4 vs. 101.9°F ± 1.7, respectively, all $p < 0.01$]. Additionally, in a large study by Mehr *et al.*, only 44% of nursing home patients with possible or probable pneumonia noted on a chest radiograph had a temperature ≥ 38°C. Thus, it seems that many elderly patients with nosocomial pneumonia do not mount a fever in response to infection. Elderly patients with pneumonia but without fever are an important population that would be excluded.

Furthermore, the studies that provide the historical evidence of the antibiotic effect did not require all three clinical criteria to be present and this requirement is not consistent with how nosocomial pneumonia was diagnosed in [Alvarez, Lerma, Fink, Rubinstein, West, Wunderink].

Suggested action: As appropriate chest radiograph abnormalities are required for patient eligibility, allow two of three clinical criteria as sufficient for patient enrollment.

Lines 292-293: **In addition, patients with VABP should have a Clinical Pulmonary Infection Score of greater than 6**

Cubist comment: Pugin *et al.* developed the original CPIS to improve the clinical diagnosis in VABP. The CPIS combined clinical, radiographic, physiological, and microbiological data into a single score that was evaluated retrospectively. The range of possible scores was 0 to 12 points. The authors concluded that a score >6 correlated well with the presence of pneumonia; however, the score was not validated by the authors at that time and there was no retrospective review to evaluate the original data and adjust their score to better refine its accuracy on the basis of their observations [Zilberberg]. Additionally, the original CPIS required tracheal aspirate culture results, rarely available at study entry, and hence could not be used prospectively as a screening/diagnostic tool in VABP.

Singh *et al.* developed a modified CPIS, applied at three days post-dose, to curtail unnecessary antibiotic use in VABP. The modified CPIS assessed temperature, blood leukocyte count, tracheal secretions, oxygenation, and character of pulmonary infiltrate at baseline. The range of possible scores at baseline was 0 to 10 points. The CPIS on day 3 was based on the aforementioned variables and in addition, took into consideration the progression of pulmonary infiltrate and available culture results from the tracheal aspirate. The range of possible scores on day 3 was larger (0 to 14 points) than at baseline, accounting for additional information obtained after baseline. Thus a score of >6 on day 3 did not have the same significance as the same score at baseline. A CPIS >6 on day 3 was considered to be suggestive of ongoing pneumonia. In that study, patients with a modified CPIS ≤6 at baseline were randomized to receive standard treatment (10-21 days of antibiotic treatment chosen by the investigator) or 3 days of ciprofloxacin monotherapy and then re-evaluated on day 3. If their CPIS was still ≤6, antibiotics were discontinued; however, if their CPIS was >6 they were considered to have unresolving pneumonia. Those with unresolving pneumonia continued ciprofloxacin therapy or had their medication changed based on available microbiological data. This study, while suggesting that

the modified CPIS may be a tool to guide physicians' prescribing of antibiotics, does not validate the use of the modified CPIS at baseline as a diagnostic tool.

In addition to the logistical challenges of utilizing a CPIS as a prospective diagnostic tool, subsequent studies have found that the diagnostic sensitivity and specificity of a CPIS is limited [Fabergas, Croce, Pham, Luyt, Lauzier]. The table below summarizes the findings of these studies:

Author, Year	Total Points Possible	Reference Standard	Application	Sensitivity	Specificity
Fabergas, 1999	12 (Pugin score)	Post-mortem sputum sample and lung biopsy	Attempt to validate the CPIS	77%	42%
Croce, 2006	10 (Simplified CPIS from Luna et al.)	Quantitative cultures of BAL[a] effluent	Use as a diagnostic tool in a trauma population	61%	43%
Pham, 2007	10 (Singh score)	Quantitative cultures of BAL effluent	Use as a diagnostic tool in burn patients	30%	80%
Luyt, 2004	10 on Day 1, 14 on Day 3 (Singh score)	Quantitative cultures from BAL or PSB[b]	Decrease unnecessary antibiotic use based on Day 3	89%	47%
Lauzier, 2008	10 (Singh score)	Quantitative BAL or qualitative ETA[c]	Relationship between baseline CPIS and VABP diagnosis	Not reported*	Not reported*

[a]broncheoalveolar lavage, [b]protected specimen brush, [c]endotracheal aspirate
*Sensitivity and specificity not reported; however, the area under the receiver operating characteristic curve for the CPIS was low (0.47), indicating no clinically useful information

Thus, the clinical utility of using a CPIS >6 as a surrogate marker for the presence of VABP and as entry criteria in a clinical trial appears both insensitive and poorly specific and thus would not provide greater diagnostic assurance. This is especially true because most of the measurements that make up the CPIS are captured under other required entry criteria (e.g., fever/hypothermia, leukocytosis/leukopenia, respiratory secretions and pulmonary radiography).

Suggested action: Allow sponsors to include CPIS as an assessment of clinical progress rather than requiring its use at baseline as a diagnostic tool for patient enrollment.

Lines 375-376: **Exclusion criterion: Patients who have received prior antibacterial drugs within the past 30 days with activity against bacterial pathogens that cause HABP/VABP**

Cubist comment. Per the draft guidance and other sources, a hospital stay of ≥48 hours places patients at risk for developing a nosocomial infection. This definition implies that nosocomial infections, including HABP/VABP, have an incubation period of less than 48 hours. This in turn, implies that antibiotics given prior to the incubation period would not be expected to impact the

response to therapy of the patients' current infection. Pertel *et al.* showed in the daptomycin trials for CAP, that recent administration of effective antibiotics (up to 24 hours before enrollment) could mask poorly effective therapy, but an effect was not noted beyond that administration window. The population at risk for, and likely to develop, HABP/VABP is often cared for in the intensive care unit where antibiotics are routinely given to >60% patients, regardless of infection status [Bergmans, Zavasky, Roder, Ibrahim]; making enrolling ICU patients without any previous antibiotic use in the prior 30 days extremely challenging. Clinical trials previously conducted in nosocomial pneumonia have excluded systemic antibiotic therapy given for >24 hours immediately prior to randomization (unless failure of previous treatment is documented), and among those who met the criteria for inclusion, rates of antibiotic use were in excess of 50% (telavancin 52% and vancomycin 57%, p=0.09) [Rubinstein]. Clearly, if patients who received > 24 hours of prior antibiotic therapy were included, the proportion would be substantially greater.

Although the use of prior antibiotics can have an effect on pathogen susceptibility and risk of resistance, literature exists documenting a significant increase in the incidence of fatal outcomes in patients who had received prior antimicrobial therapy before the onset of pneumonia as compared with those who had not, which would enrich for the intended population at a 20% risk of mortality. In a study by Fallon *et al.*, 83% of the 31 patients who had received prior antimicrobial therapy within 10 days of the onset of pneumonia died, as compared with only 48% of patients who had not ($p<0.01$). These findings were further supported by Rello *et al.*, where 27.8% of patients who had received prior antimicrobial therapy for more than 48 hours in the 10 days preceding onset of VABP died, compared with only 4% of those who did not ($p=0.0001$).

We believe that seeking the ideal unconfounded study population would be at the cost of excluding the majority of patients with HABP/VABP, resulting in an entirely non-representative study population and studies that are not feasible to conduct. We also feel that it is inappropriate to extrapolate findings observed in the daptomycin CAP trial, where *S. pneumoniae* was the primary pathogen, to more hardy pathogens such as *Pseudomonas* or *S. aureus*.

Suggested action: Allow less than 24 hours of prior short-acting non-study antibiotic use. Also, we ask the Agency to examine data from prior pivotal submissions in this indication to investigate the potential confounding effect of prior antibiotic therapy, and share the highlights of this analysis with Sponsors and other interested parties to help understand the basis for this restrictive requirement.

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Sincerely,

David S. Mantus, Ph.D.
Vice President, Regulatory Affairs

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Document Details

David Shlaes - Comment

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In their recently-released Draft Guidance on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment, the FDA suggests that patients at high risk of dying (those with APACHE scores of 15 or greater) be enrolled to allow for a treated mortality rate of around 20%. That would allow for a non-inferiority margin of 10%. BUT – the analysis population is the microbiology intent to treat (MITT) population – that is, those patients enrolled and treated who have an identified bacterial pathogen at study entry. If the mortality rate is less than 20%, the FDA suggests using an NI margin based on an odds ratio calculation that should be discussed with the agency. At the AIDAC where this was discussed, a figure of 1.67 was discussed. This equates to an NI margin of about 5.7%.

Once again, in the appendix to the guidance, the FDA has gone to extraordinary and unscientific lengths to discount the treatment effect of antibiotics in VAP such that they arrive at an infeasible trial design. They demonstrate that inappropriate therapy for VAP is associated with a 62% mortality and that appropriate therapy is associated with a 20% mortality. The treatment effect of appropriate vs. inappropriate therapy is, therefore, 42%. Of course, inappropriate therapy is not no therapy, and 42% as a treatment effect is therefore already conservative. But, the FDA is not satisfied with that. They go on to apply their 95/95 rule using the upper bound of the 95% confidence interval for treatment effect of inappropriate therapy and the lower bound for appropriate therapy yielding a treatment effect of 29% instead of 42%. They then discount the treatment effect of 29% by an additional 30% for good measure. The FDA justifies their additional 30% discount by claiming that this is necessary to correct for "uncertainties" of the historical database. This brings the treatment effect or M1 down to 20%. How convenient! They now take 50% of that and call that a justified non-inferiority margin of 10%. (Is 10% starting to sound like a familiar number?) But since the margin simply has to be smaller than the treatment effect, the margin could just as easily have been 19%. But of course the entire discounting argument is overly conservative and irrational.

I have been trying to understand the practical consequences of this design. Lets take VAP since the FDA seems to focus on VAP in their guidance. In my calculations I have made the following assumptions:

Cure rate = 80% (20% mortality).

Evaluability – as far as I can tell, in modern trials, the MITT population is about 50% of the enrolled population.

NI margin = 10%

90% power (to exclude the chance of falsely concluding inferiority as much as possible).

I calculate that one would need to enroll 747/arm or 1494 per study for a total of 2988 subjects. For an 80% powered study, which would double the chance of falsely concluding non-inferiority, 2012 subjects would have to be enrolled. For an NI margin of 5.7%, 4640 and 3480 subjects would have to be enrolled for a 90% or an 80% powered trial respectively.

Based on recent experience, including that of the ATTAIN-1 and -2 trials by Theravance/Astellas, modern enrollment rates for microbiologically documented patients are on the order of 0.1 subjects per center per month. Therefore, for the two trials noted above, given a record 300 centers for each trial, the required studies would take 5.5 to 8 years to enroll. For the NI margin 5.7% trials, assuming less than 20% mortality as is common in modern trials, 10 to 13 years would be required. Respectfully – these proposals are madness, especially in a time of high medical need in these indications.

In terms of cost, VAP trials are probably the most expensive trials we currently undertake. If costs are $50-100,000 per evaluable patient, a 2400 patient set of trials in VAP would cost $120-240 million. No company let me repeat that, NO COMPANY will take this on! These costs rapidly outstrip any return on investment.

This guideline should be immediately rescinded and replaced with guidance requiring a feasible trial design.

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Document Details

David Shlaes - Comment

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1. NI Margin – as this becomes more relaxed – lots of good reasons to do this – everything else gets easier.
    a. Please provide numbers required for studies where mortality is lower than 20%.
2. APACHEII now underestimates mortality and scores higher than 15 will be required to assure mortality greater than 20%.
3. Proscription against antibiotics – most commonly cited problem for infeasibility and probably unnecessary. Also will exclude those patients you most want to include.

Perlel *et al.* showed in the daptomycin trials for CAP, that recent administration ()f effective antibiotics (up to 24 hours before emoUment) could mask poorly effective therapy, but an effect was not noted beyond that administration window. The population at risk for, and likely to develop, HABP/V ABP is often cared for in the intensive care unit where antibiotics are routinely given to >60% patients, regardless of infection status [Bergmans, Zavasky, Roder, Ibrahim]; making enrolling ICU patients without any previous antibiotic use in the prior 30 days extremely challenging. Clinical trials previously conducted in nosocomial pneumonia have excluded systemic antibiotic therapy given for >24 hours immediately prior to randomization (unless failure of previous treatment is documented), and among those who met the criteria for inclusion, rates of antibiotic use were in excess of 50% (telavancin 52% and vancomycin 57%, p=0.09) [Rubinstein]. Clearly, if patients who received> 24 hours of prior antibiotic therapy were included, the proportion would be substantially greater.

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1. *Suggested action:* Allow less than 24 hours of prior short-acting non-study antibiotic use. Also, we ask the Agency to examine data from prior pivotal submissions in this indication to investigate the potential confounding effect of prior antibiotic therapy, and share the highlights of this analysis with Sponsors and other interested parties 10 help understand the basis for this restrictive requirement.

4. Mortality as an endpoint is insensitive and irrelevant to clinicians treating the disease.
5. VAP is a disappearing disease – probably related to better care plus significant recent underreporting in the US under pressure from CMMS reimbursement guidelines. Therefore, special consideration should be given to the fact that there is a small and shrinking population available for study even though the medical need in this population is greatest. SEE J&J DOCKET SUBMISSION.
6. Inclusion of HCAP per Cubist?

SOLUTIONS

1. Admit that diagnosis is difficult and a *perfect* rationale for the NI margin in this disease does not exist nor does a *perfect AND feasible* trial design and go on from there. Allow the use of endpoints - mortality, OR clinical outcome OR clinical outcome plus survival at 28 days as a composite.
2. Allow the use of PK/PD measures to justify a margin for clinical benefit as determined by extrapolations to no therapy and/or comparing inappropriate to appropriate therapy.
3. Increase the margins to something more reasonable – 15%. Forget the odds ratio method constraint.
4. Allow the use of up to 24 hours of an antibiotic at the time of enrollment.
5. Discard the proscription against any antibiotic within the previous month.
6. Consider the inclusion of HCAP patients where HAP/VAP pathogen is documented.

February 28, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment [Docket No. FDA-2010-D-0589]

Dear Sir/Madam:

Pfizer, Inc. is providing comments on the above-referenced draft guidance on "Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment" that was published in the *Federal Register* of November 29, 2010 (75 FR 73107).

We appreciate the opportunity to comment on this draft guidance and trust that the Agency will take these comments into consideration. Accordingly, please refer to the attached table of comments/recommendations.

Please do not hesitate to contact the undersigned if there are any questions or if clarification is needed.

Sincerely,

Nadia D Kirzecky

Nadia Kirzecky
Director, Worldwide Regulatory Strategy
212-733-9110

Attachment

FDA DRAFT GUIDANCE -- "HOSPITAL-ACQUIRED BACTERIAL PNEUMONIA AND VENTILATOR-ASSOCIATED BACTERIAL PNEUMONIA: DEVELOPING DRUGS FOR TREATMENT" [Docket No. FDA–2010–D–0589]

COMMENTS FROM PFIZER

1. GENERAL COMMENTS

GENERAL COMMENTS
• It is expected that sponsors will generally conduct these studies on a worldwide basis. It is therefore critical to keep in mind that global development programs will look to harmonize protocol designs, and that a single primary end point of all-cause mortality may not address regional guidelines and guidances in indications in HABP/VABP. • Furthermore, a sole primary end point of all-cause mortality is a potential impediment in facilitating clinical development in the treatment of HABP/VABP. The numbers of patients that would need to be enrolled could theoretically run into the thousands, therefore, rendering the execution of such studies within a reasonable timeframe both unfeasible and impractical. Moreover, effective preventive measures, along with other factors have decreased the incidence of nosocomial pneumonia in the U.S. As a result, recruitment in these trials can be low (e.g., ~0.2 patients per center per month).[1] We therefore recommend that the Agency also consider other clinical outcomes that are relevant to the treatment of HABP and/or VABP to facilitate meeting the unmet medical need in this clinical setting. In addition, while recognizing potential slow patient recruitment, we ask the Agency to consider the reliance of a single adequate and well-controlled study for supporting effectiveness under certain circumstances, such as the availability of clinical data from other approved indications. • The definition and diagnosis of HABP is limited with regards to the context of the draft guidance. The inclusion of HCAP patients needs to be re-considered e.g., in the context of bacterial etiologies that do not differ from HABP/VABP such as MRSA and Gram-negative species. Furthermore, the definition and diagnosis of pneumonia seems stricter within the context of the draft FDA guidance when compared to CDC criteria, etc. Fever/hypothermia and leukocytosis, with or without a left shift, are not essential for the diagnosis of nosocomial pneumonia and are nonspecific findings that may be seen in a variety of noninfectious disorders. In addition, fever may not always be present in all HABP/VABP patients, for example the elderly. • Guidance should be provided for clinical trials that will use/assess rapid diagnostic tests. For example, if the pathogen is identified quickly, the restrictions in the draft guidance concerning HCAP become moot. • There is a need to include requirements for indications against resistant organisms (i.e., number of organisms required for MRSA, etc.). • Guidance should be given on study design to assess appropriate duration of treatment. Although 7 days of treatment appears to be effective for VABP, currently the appropriate duration of treatment of HABP and VABP are not clearly known. There are no recommendations in the draft guidance on the duration of treatment. • See further details below.

[1] FDA Transcript of March 31, 2009 and April 1, 2009 Public Workshop on Clinical Trial Design for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

FDA DRAFT GUIDANCE -- "HOSPITAL-ACQUIRED BACTERIAL PNEUMONIA AND VENTILATOR-ASSOCIATED BACTERIAL PNEUMONIA: DEVELOPING DRUGS FOR TREATMENT" [Docket No. FDA–2010–D–0589]

2. SPECIFIC COMMENTS ON TEXT

Page and Line No.	Comment and Rationale	Proposed change (if applicable)
Page 4, Lines 121-125	In the draft FDA guidance, HCAP or pneumonia among persons residing in chronic care facilities such as nursing homes is not considered to be HABP. However the microbial etiology of nursing home pneumonia encompasses both microbes associated with CAP and those associated with nosocomial pneumonia (El Sohl (Semin Respir Crit Care Med 2009; 30: 016-025).	The patient population definition should be revised to include nursing home/LTCF patients when the goal of the clinical trial is to examine the effectiveness of a drug against a specific organism associated with HABP such as MRSA or Gram-negative species. Proposed Change "The more general term *health care-associated pneumonia*, or pneumonia among persons residing in chronic care facilities such as nursing homes, is generally not considered to be HABP as defined in this guidance because the bacterial pathogens in these patients with the broader category of health care-associated pneumonia are, in general, less likely to be similar to bacterial pathogens in patients with HABP/VABP. However, these patients could be included when the goal of a clinical trial is to examine the effectiveness against a specific organism associated with HABP that is also associated with the microbial etiology of pneumonia in patients living in chronic health care facilities (such as nursing home patients)."
Page 5, Lines 175-188	The draft guidance explicitly identifies and discusses the number of clinical trials needed to support a HABP/VABP indication when it is the sole indication sought. Lines 175-176 appear to imply that two trials in HABP/VABP may not be needed to support a HABP/VABP indication if the overall drug development program includes other relevant indications that may be filed in conjunction. If that is the intended meaning of Lines 175-176 and only one trial may be sufficient, then does the Agency recommend that the single trial only enroll VABP patients to support the HABP/VABP indication?	Please clarify in the final guidance.
Page 7, Lines	The FDA draft guidance recommends that chest X-ray (CXR) should have a new	Proposed Change

FDA DRAFT GUIDANCE -- "HOSPITAL-ACQUIRED BACTERIAL PNEUMONIA AND VENTILATOR-ASSOCIATED BACTERIAL PNEUMONIA: DEVELOPING DRUGS FOR TREATMENT" [Docket No. FDA–2010–D–0589]

Page and Line No.	Comment and Rationale	Proposed change (if applicable)
254-255	infiltrate characteristic of bacterial pneumonia. CXR is not sensitive or specific for the diagnosis of bacterial pneumonia (Klompas M. JAMA 2007; 297). However presence of multilobar pneumonia is associated with severe HABP (Campbell GD et al. Am J Respir Crit Care Med 1996; 153).	"The chest radiograph should show the presence of ***new*** infiltrate(s) ~~characteristic of~~ compatible with bacterial pneumonia. The final full report of the chest radiograph…, and should state the extent of involvement (i.e. single vs. multilobar as well as the presence of pleural effusion) to assess disease severity."
Page 7, Lines 262-273	The FDA draft guidance "requires" patients to have fever/hypothermia, abnormal WBC, bandemia and new onset purulent secretions to be eligible. This guidance appears limited and based on criteria published in 1972 in Sun Intern Med by Johanson WG Jr et al. Fever/hypothermia and leukocytosis, with or without a left shift, are not essential for the diagnosis of nosocomial pneumonia and are nonspecific findings that may be seen in a variety of noninfectious disorders. Presence of new respiratory secretions is not specific for VABP (Klompas M et al Ann Int Med 2007; 147). In addition, HCAP due to different pathogens have different patient risk factors and clinical presentations.	The strict definition and diagnosis of pneumonia in the draft FDA guidance should be revised in the final guidance to more closely match the CDC surveillance definition for clinical diagnosis of HAP criteria (Klompas M et al Ann Int Med 2007; 147). For example, fever/hypothermia and leukocytosis, with or without a left shift, are not essential for the diagnosis of nosocomial pneumonia and are nonspecific findings that may be seen in a variety of noninfectious disorders. Moreover, it is expected that HABP/HAVP trials will most likely enroll a majority of elderly patients who tend to have either no or a low elevated body temperature, and thus fever is not an appropriate criterion for elderly patients in the context of a HABP/VABP trial.
Page 8, Lines 292-293 and 301-310	The FDA draft guidance recommends including a clinical severity scoring system to assure that the clinical trial population has a high likelihood of mortality. APACHE and CPIS scoring systems are suggested. However these scoring systems have limitations. For example, an APACHE score may be low in a severely ill patient who is young, while a CPIS score may be low in a patient who does not have fever or high WBC.	The final guidance should reflect that data should be collected on the presence of baseline bacteremia, duration of ventilation prior to the enrollment, presence of rales and hypoxemia, admission to ICU, presence of sepsis/hypotension. Patients should be characterized as medical, surgical or trauma. The sensitivity and specificity of CPIS score can be enhanced by using it together with Gram stain, radiographic response, improvement in minute ventilation, and clearance of bacteria in cultures (Fartoukh MB et al. Am J Respir Crit Care Med 2003; 168:173).

FDA DRAFT GUIDANCE -- "HOSPITAL-ACQUIRED BACTERIAL PNEUMONIA AND VENTILATOR-ASSOCIATED BACTERIAL PNEUMONIA: DEVELOPING DRUGS FOR TREATMENT" [Docket No. FDA–2010–D–0589]

Page and Line No.	Comment and Rationale	Proposed change (if applicable)
Pages 10-11, Lines 375-376 and Lines 423-425	The exclusion of patients "who have received prior antibacterial drugs within the past 30 days with activity against bacterial pathogens that cause HABP/VABP" represents a seemingly improbable situation, as virtually all patients in this clinical setting will most likely have received some antibacterial therapy beforehand. The preferred population of sick patients with an APACHE score > 15 is by definition a heavily pretreated population, and in recent VABP trials about half of the patients had antibiotics in the prior 10 days.	In this patient population, administration of prior antibiotics within a 30 day window is expected in the treatment of an acute illness. These antibiotics are generally short-lived and thus not expected to have any impact on the pneumonia under study. Please revise the guidance accordingly.
Pages 10-11, Lines 412-419	The requirement for the use of FDA-approved active comparators is overly restrictive as some agents, such as meropenem that are used for HABP/VABP do not have this indication. Furthermore, it is expected that these studies will enroll subjects globally and local standards-of-care to treat HABP/VABP may include non-FDA approved comparators. Thus, we propose that comparator(s) should be FDA-approved, or standard of care, or well defined in HABP/VABP treatment guidelines.	Proposed Change: "Placebo-controlled trials that do not incorporate antibacterial treatment for HABP/VABP are not appropriate for this indication. In general, it is recommended that ~~The~~ the active comparator(s) should be an antibacterial drug at the recommended dosage that is FDA-approved for treatment of 'nosocomial pneumonia' or 'HABP/VABP' or is FDA-approved for the treatment of 'lower respiratory tract infections' with the appropriate antibacterial spectrum for pathogens encountered in HABP/VABP. Ideally, the comparator drug selected would also be a drug recommended in current treatment guidelines for HABP/VABP. However, other active comparators (e.g., agents listed in the current treatment guidelines for HABP/VABP, but not specifically approved for HABP/VABP) can also be considered depending on study design, etc. Sponsors should discuss with the FDA the choice of the control antibacterial drug if the drug is not FDA-approved for ~~'lower respiratory tract infections'~~ HABP/VABP. ~~Ideally, the comparator drug selected would also be a drug recommended in current treatment guidelines for HABP/VABP.~~"
Pages 11-12,	Based on current treatment guidelines, the use of monotherapy in the context of	Please clarify in the final guidance.

FDA DRAFT GUIDANCE -- "HOSPITAL-ACQUIRED BACTERIAL PNEUMONIA AND VENTILATOR-ASSOCIATED BACTERIAL PNEUMONIA: DEVELOPING DRUGS FOR TREATMENT" [Docket No. FDA–2010–D–0589]

Page and Line No.	Comment and Rationale	Proposed change (if applicable)
Lines 454-457	treating patients with HABP/VABP seems impractical or inappropriate to cover the potential spectrum of pathogens in this disease.	
Page 12, Line 464	The primary endpoint of all-cause mortality within 28 days after randomization makes the feasibility of enrolling sufficient subjects to conduct such a study within a reasonable timeframe "virtually" impossible. Niederman has recently suggested that if superiority is a goal of trial design, end points could be microbiologic eradication, time to microbiologic eradication, prolonged duration of therapy, need to modify initial therapy, and serial evaluation of the arterial oxygen tension to fractional inspired oxygen ratio (CID 2010 August; PMID: 20597660).	Primary endpoints other than all-cause mortality in the treatment need to be considered. Mortality can be a component of a composite end point. For example, if the study achieves noninferiority for 30-day mortality, superiority end points could be microbiologic eradication, time to microbiologic eradication, prolonged duration of therapy, need for oxygen support, and need to modify initial therapy.
Pages 12-13, Lines 490-496	The requirement for a validated patient-reported outcome (PRO) measurement to defend clinical endpoints that include symptoms seem unrealistic in a patient population that is obtunded, sedated, ventilated, etc. Additionally, there are currently no PROs for this condition.	Please clarify in the final guidance.
Page 14, Lines 566-567	Obtaining blood culture samples from two separate venipuncture sites is too demanding, especially for a very sick and older patient population.	
Pages 16-17, Lines 659-668	It is unclear how the fixed noninferiority margin of 1.67 based on an odds ratio metric is obtained for a mortality rate less than 20%. If one assumes a 10% margin for the rate difference in the boundary case when the mortality rate in the active control group is 20%, this means that the mortality rate could be 30% for the new treatment. The latter translates to an odds ratio for mortality (new treatment vs. active control) of 1.71.	Please clarify how the 1.67 odds ratio was obtained.
Pages 17, Lines 672-677	The draft guidance acknowledges variability in the mortality rate in the active control group. Consequently, the required sample size will be a function of the mortality rate in the control group and thus, blinded sample size re-estimation on the mortality rate should be encouraged.	The draft guidance should address the role of sample size re-estimation in light of varying mortality rate in the active control group.

Page and Line No.	Comment and Rationale	Proposed change (if applicable)
	How should the protocol handle the two different margin pathways prospectively? Does the 20% mortality rate correspond to the "observed" mortality rate in the active control group at the end of the trial? The type I error rate under this result-driven strategy could exceed 5% on some occasions based on the usual confidence interval approach for non-inferiority.	The draft guidance should examine the statistical property of a decision rule that is data dependent.
Page 27, Lines 969-973	No explanation/rationale is provided for the 30% reduction of the 29% treatment effect and a further 50% reduction of that number to arrive at the 10% M2 value listed on Line 989.	Please clarify in the final guidance.

February 28, 2011

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Division of Dockets Management
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HFA–305, Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Response to FDA Request/Comment
General Correspondence: Comments on Draft Guidance for Industry: Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment
[Docket No. FDA–2010–D–0589]

Dear Sir or Madam:

Reference is made to the notice published by FDA in the Federal Register on November 29, 2010 to invite written comments on a "Draft Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment". The purpose of this submission is to provide comments from GlaxoSmithKline (GSK) on this draft guidance.

GSK is a research-based pharmaceutical and biotechnology company. Our company is dedicated to the discovery, development, manufacture and distribution of medicines and vaccines that enable people to lead longer, healthier and more productive lives. We appreciate the opportunity to comment on this draft guidance, as GSK has a long history of developing antibacterial agents for the treatment of patients with infectious diseases such as pneumonia.

The comments listed in the table below begin with overall comments on the draft guidance, followed by specific comments identified by page, section, and line number, where applicable.

Page/ Section/ Paragraph/ Line No	Comment (with rationale)	Proposed change
General comments		
Regarding 20% mortality rate for NI parameters	This level of mortality is hard to protocolize into eligibility requirements. The patients are either demonstrating signs of organ dysfunction, or (in historical studies) experienced delays in getting proper antibiotics, many patients will have late onset VAP and less likely not to have received or receiving other antibiotics. Very much less likely to be a HABP patient unless quite septic.	We think it will be very challenging to target a population at 20% and we need to better understand what options may exist if the mortality is actually between 15-20% (as many subjects will have volunteered for the study and one can't predict the comparator mortality rate early on in the study.) It must also be realized that many of the deaths seen in a clinical trial will not be attributable to the pneumonia, and variability around non-attributable mortality will carry a significant influence in the study. This is a very high risk. Is there some way that FDA can validate eligibility criteria that would recruit this target population?
Regarding HAPB studies	In addition to the low likelihood that these subjects will have 20% ACM, it is also very difficult to obtain adequate specimens to do quantified microbiology.	Please acknowledge the challenges and offer your perspectives on the microbiology criteria in HAPB.
Regarding microbiologic endpoints	Microbiologic endpoints are not mentioned in the guidance document.	Can the Agency provide their current thinking on the appropriateness of microbiology endpoints in HABP/VABP trials?
Regarding 'all cause mortality' terminology	In many places in the guidance document the term all cause mortality within 28 days is used. Since the actual measurement is at 28 days, it is suggested that the word 'within' be replaced by 'at'.	Suggest the term all cause morality at 28 days be consistently used in the guidance document
Specific comments		
Page 4, Line 131	Change "and" to "or" between *K. pneumoniae* and non-Enterobacteriaceae – activity against both of these is not a requirement.	To read: Gram-negative Enterobacteriaceae such as *K. pneumoniae* or non-Enterobactericeae...

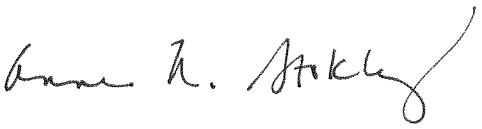
Page/ Section/ Paragraph/ Line No	Comment (with rationale)	Proposed change
Page 4, Lines 138-147	Can the guidance document provide some background data on how many patients with suspected/ clinically diagnosed VABP/ HABP actually have a positive culture (i.e. if it takes 200 clinical subjects to provide 40 qualifying (via epithelial cells counts, etc.) bacterial isolates; this information would provide more guidance on the number of subjects that would be required to be screened.	Provide the requested background information.
Page 5, Lines 151-161	The guidance document indicates what types of studies are needed in special populations but does not mention drug interaction studies. Because of the need to enrol elderly patients in the HABP and VABP studies guidance on what types of drug interactions is desirable.	Include information on what drugs (or drug classes) such be studied with respect to drug interactions and when such studies are required in relation to the start of Phase 3 trials.
Page 5, Line 157	Geriatric, as a special population, may need to be defined by either age or functional health status; page 6, line 211 uses >65 years.	Better define the 'advanced age category'.
Page 5, Line 168	Change "and" to "or" between *K. pneumoniae* and non-Enterobacteriaceae – activity against both of these is not a requirement	To read: as MRSA or Gram-negative Enterobacteriaceae such as *K. pneumoniae* or non-
Page 5, Lines 168-169 and Pages 6-7, Lines 239-240	There are only three Gram negative organisms specifically listed. Does this suggest that FDA does not consider *Enterobacter* spp as a significant pathogen in HAPB/VAPB?	It should be made clearer if FDA is allowing any Gram negative *Enterobacteriaceae* and what pathogens FDA considers relevant to the HAPB/VAPB indications
Page 5, Lines 175-188	Should the guidance mention the relevance or lack of relevance of CABP studies when determining whether two pivotal clinical trials are required?	Clarify whether or not conducting a Study in CABP has any impact on the need to conduct two clinical trials in HABP/VABP
Page 6, Lines 205- 208	Do AEs not related to the drug have to be followed outside of study periods?	Clarification is requested.
Page 9, Lines 345-349	There is no mention of identifying pathologic bacteria from routine sputum.	Add example method for determination of pathological bacteria from sputum.

Page/ Section/ Paragraph/ Line No	Comment (with rationale)	Proposed change
Page 9, Lines 346-349	Thresholds of bacterial growth has been defined for protected brush specimen (10^3 CFU/mL) and for endotracheal aspiration (10^6 CFU/mL), but not for sputum (deep expectoration) or bronchoalveolar lavage sampling.	Add thresholds of bacterial growth for sputum (deep expectoration) or brochoalveolar lavage sampling.
Page 10, Line 375	Excluding patients who receive antibiotic treatment for 30 days is unjustified and will invalidate many HAP/VAP patients.	Most patients with this target mortality will have received antibiotics in the previous 30 days, consider a shorter timeframe. Thus, this exclusion criterion should be eliminated.
Page 10, Lines 398-399	Stratification by age and 'location in hospital' (Location in hospital will have variability from one site to another such as tertiary care hospitals vs. community hospitals).	Stratification should be made by age and severity of illness.
Page 10, Line 403	Include patients of 'both sexes and all races'. What about ethnicity?	'Revise to; 'both sexes and all races/ethnicities.'
Pages 11-12, Lines 431-460	It is unclear how FDA will handle situations when a physician uses a drug that is not approved for LRTI but is used as a standard of care in situations where there is a high level of resistance (i.e. amikacin).	Clarify if drugs used in common practice (but which are not specifically approved for LRTI's) to treat resistance pathogens (seen with GNR VAPB) can be utilized in HAP studies?
Pages 11-12, Lines 433-460	It is considered likely that there will be a need for additional antibiotics until pathogen confirmation is obtained (i.e. Gram negative antibiotic will require addition of Gram positive coverage until pathogen confirmed).	Clarify if early antibiotic treatment can be made with an approved antibiotic until pathogen test results are know? If so, what is there a maximum duration?
Page 17, Lines 665-667	The draft states 'For clinical trials with observed active control mortality rate of less than 20 percent, a fixed noninferiority margin of 1.67 based on an odds ratio metric should be used.' This is clearly a data-driven analysis. If the study protocol specified the primary analysis using the risk difference metric, which analysis will FDA consider as the primary analysis in your data review?	Add additional clarification.

Page/ Section/ Paragraph/ Line No	Comment (with rationale)	Proposed change
Page 17, Section 12, Part c. "Sample size"	It would be helpful if the document actually ran a typical sample size...estimating how many subjects would be needed if an active comparator did indeed have an 80% "survival' at 28 days, and let say a test drug has survival rates of 85%, or 90%"....with 10% LCI, what is the N in each arm.	Add additional clarification/example.
Page 19, Lines 745-752	Describing the results of the 'all cause morality' (the primary endpoint) is not very informative to Health Care Providers (HCPs) as the reality is that antibiotic treatment (with an approved antibiotic) for a serious disease will positively affect survival. Secondary endpoints such as clinical cure or clinical improvement are considered very informative by HCPs.	Clarify if secondary endpoints can be described in the Clinical Trials section of the product labelling.
Page 22, Appendix A, Table 1	Consider addition of Kett observational study (Kett DH, et al. Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACT-HAP) Investigators. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis.* 2011 Jan 19.)	Compliant IDSA/ATS guideline group (= 2 gram-negative drugs and MSRA coverage) had 35% mortality vs. 21% in noncompliant group); high mortality with *Pseudomonas* and MRSA in the compliant group while in noncompliant group this was not true for *Acinetobacter* and *Klebsiella*. Part of the definition of compliance was that all drugs were used and there wasn't de-escalation.
Pages 24-25, Appendix A, Lines 880-916	All cause mortality >20% is considered unlikely with HABP.	Revise to a more realistic value for HABP.
Page 24, Appendix A, Lines 882-895	In many centers, ACM for VAP is 10-15%, unless patient displaying signs of organ failure associated with sepsis.	Revise ACM value to a more realistic value.
Page 23 and 25, Appendix A, Lines 876-878 & 915-916	Use "%" instead of percentage (as per Table contents).	Revise format to use "%".

Again, we appreciate the opportunity to provide comments on this draft guidance. Please contact Edward Yuhas at (610) 787-3689 for any clarification needed. This submission is provided in electronic format according to the instructions provided at http://www.fda.gov/RegulatoryInformation/Dockets/Comments/ucm089193.htm

Sincerely,



Anne N. Stokley, M.S.P.H.
Senior Director, Policy, Intelligence & Education
Global Regulatory Affairs

AstraZeneca

February 28, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number FDA-2010-D-0589
Response to FDA Call for Comments
Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment

Dear Sir or Madam:

Reference is made to the November 29, 2010 Federal Register notice announcing the request for comments on "Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment"

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Cindy M. Lancaster, US Executive Director, Regulatory Affairs, at (302) 885-1348.

Sincerely,

Darci L. Bertelsen /DV

Darci L. Bertelsen,
Regulatory Affairs Director,
Telephone: (302) 886-7355
Fax: (302) 886-2822

DLB

Enclosure

Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

[Docket No. 2010-D-0589]
Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
3	105-109 121-125	At lines 105 to 109, 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.* AstraZeneca agrees that patients should be considered to have HABP-VABP only if they are likely infected with isolates typical of that syndrome, but ideas such as "in a hospitalized patient" are less clear now than in the past due to evolution of health care systems. For example, AstraZeneca proposes that a patient in a chronic care facility with HABP or VABP when on a ventilator might be an acceptable candidate for enrolment in clinical trials. To allow for appropriate interpretation of what clinical sites would be acceptable, we suggest that guidance indicate that Sponsors should document the relevance of the site of enrolment. Restricting enrolment to the settings described in draft guidance is one such approach, but a Sponsor might logically propose inclusion of other populations by demonstrating the concordance of the situation, syndrome, and microbiology to the expected patterns of infection. AstraZeneca proposes the following revision in the guidance (see bolded text): For lines 105-109, "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. **Patients from other settings (e.g., a chronic care facility) could be considered for enrolment if the sponsor**

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		documents the concordance of the HABP-VABP syndrome in patients from that setting with the syndrome noted in patients meeting the general rules for hospitalization." For lines 121-125, "The more general term *health care-associated pneumonia*, or pneumonia among persons residing in chronic care facilities such as nursing homes, is not considered to be HABP as defined in this guidance because the bacterial pathogens in these patients with the broader category of health care-associated pneumonia are, in general, less likely to be similar to bacterial pathogens in patients with HABP/VABP **and, therefore, sponsors must provide appropriate documentation about the patients enrolled and, just as importantly, the clinical sites participating in clinical trials."**
5	169-171	Culture techniques are inadequate to allow confirmation of the microbiological cause of infection in 100% of subjects. In studies targeting S. aureus, recent data suggest that only about 1/3rd of HABP and VABP patients having a syndrome strongly consistent with HABP-VABP due to a Gram-positive pathogen will have supportive microbiology (Televancin ATTAIN studies). In prior studies targeting Gram-negative pathogens, only 40-60% of subjects have had supportive microbiology (Doripenem DORI-09 and -10 studies; Alvarez-Lerma F et al. Intens Care Med 27:493-502, 2001). Further, there are substantial unresolved issues regarding culture data in HABP-VABP (e.g., relative merits of material obtained by expectoration, endotracheal suctioning, or bronchoalveolar lavage; critical CFU/ml cut-off values) that make even apparent microbiological confirmation less than certain (Barriere SL Clin Infect Dis 51(S1):S4–S9, 2010). Finally, data in the ITT population will be more representative of routine use of the drug. Thus, both approaches (microbiologically proven ITT [mMITT] vs. ITT) to selection of the primary analysis population have counterbalancing strengths & weaknesses. On balance, we feel that the ITT population has the overall advantage as the primary analysis population due to its greater relevance to future patient care and reduced dependency on specific culture technologies. Minimum numbers (or percentages) of culture-proven cases could be

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		agreed in advance. Results in the mMITT population would be used as a key sensitivity analysis and should be consistent with the results in the overall population. If the agency concludes that microbiologically proven population must be used for the primary analysis and thus for sample size calculations, the result is that the sample size for the trial must be increased by at least 2-fold and potentially as much as 3-fold. For example, 2038 patients (1019 per arm) would be required per study assuming a comparator success rate of 80%, a margin of 10%, power of 90%, and an evaluability rate of 33%. Trials of this size are costly and may not be feasible in a reasonable time frame (see also discussion below). A reasonable partial mitigation for the resulting disincentive to work in this area would be for the agency to recognize the value of both culture- and non-culture- based diagnostic tools (e.g., PCR- or antigen-based documentation of organism carriage in the blood or sputum).
5	184-5	AstraZeneca interprets the sentence at line 184, "We recommend that patients with only VABP or only HABP be enrolled in clinical trials", to mean that a given trial should enrol only either HABP or VABP (but not both in the same trial). An alternative reading is that HABP and VABP can be mixed in a given trial but that patients with other types of pneumonia (e.g., health care-associated pneumonia, FDA's comments at line 121) should not be enrolled. If AstraZeneca's interpretation is correct that the agency believes that HABP and VABP must be studied separately, such a requirement will make studies of either form of pneumonia less likely due to the increased size of numbers of patients needed to be enrolled in the trials. Recent trials have been comprised of a mixture of about 2/3rd HABP and 1/3rd VABP patients. Therefore, plans for site numbers and screening adequate to enrol only patients with HABP or VABP into a monotypic trial would need to increase 1.5-fold for a HABP-specific trial and increase 3-fold for a VABP-specific trial. Combined with the further 3-fold increase required if the primary analysis population is

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		restricted to those with microbiologically proven infection, the site number and screening requirements go up 9-fold for a single trial of VABP alone relative to past requirements for studies enrolling a mixture of HABP and VABP patients. When viewed in the context of doing one monotypic trial for each indication, the number of HABP patients needed to enrol the single monotypic HABP trial does fall by 25% relative to the numbers needed for a pair of mixed trials, but the number of VABP patients need for the monotypic VABP trial increases 50% relative to the pair of mixed trials. AstraZeneca believes that these factors could make it difficult to conduct a study in the VABP patient population. Thus, we are worried about the practical problem this represents and the fact it could hinder the pursuit of further research in this area of high unmet medical need. Provided that sponsors demonstrate supportive PK data for the two populations, comparable microbiology, and plausible severity of illness, we believe that enrolment of a mixture of HABP and VABP patients in the same trial is logical due to the overall similarity in the syndromes. Randomization and subsequently analysis should be stratified on this variable. We further urge consideration of for combined studies as we believe that providing stratified data on both indications is preferable to having data only on HABP. Clinicians will generalize from HABP to VABP — we believe that providing high quality VABP data from a prospective randomized pivotal P3 program is preferable even if the data are somewhat limited numerically. There are more similarities than differences between the syndromes and the data from the two subsets are strongly mutually supportive. If the agency continues to prefer monotypic trials for each indication, an alternative approach to the combined issue of feasibility and statistical strength is mentioned during the discussion below of M1 and M2.
5	190-193	If the oral formulation delivers the same plasma and/or lung levels of

Docket Number FDA-2010-D-0589: Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		the drug, it is our assumption that switching criteria would not be required. This should be clarified in the guidance.
8	313-321	The guidance states that patients with a bacterial pathogen isolated from respiratory secretions or blood should be eligible for inclusion in the primary analysis population. However the next statement regarding the collection of specimens, Gram staining and culturing only refer to respiratory secretions. Please revise the second sentence of this paragraph to include blood samples.
10	375-376	Please consider adding the additional text in bold. But, also note the related discussion of lines 423-9, below. "Patients who have received prior antibacterial drugs within the past 30 days with activity against bacterial pathogens that causes HABP/VABP, **unless treatment failure of the prior antibiotic can be demonstrated."**
10	398-399	The guidance is recommending stratification by age and by the location in the hospital (e.g. patients admitted to a surgical intensive care unit vs. patients admitted to a medical intensive care unit). Please include additional clarification as to how FDA would want a Sponsor to analyse and interpret these data.
11	423-429	The ability to enrol patients without prior antibiotic therapy that would be effective against bacteria that causes HABP and VABP is limited due to the substantial likelihood that patients at risk for HABP-VABP would have received antibiotics for other issues in the recent past. Indeed, it may be those very issues which place these patients at risk for developing HABP-VABP. Thus, the proposal to exclude patients who have received any active antibiotics in the previous 30 days (line 375) will make enrolment difficult, will lead to enrolment of a non-representative patient population, and will also reduce the enrolment of patients infected with higher MIC isolates. As most relevant antibiotics have a half-life measured in hours and require dosing 2-3 times daily, exclusion for use of relevant antibiotics in the previous 4 days would ensure complete clearance of active drugs.

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		Particularly if the microbiologically evaluable ITT population is used as a sensitivity assessment, it is also not logical to exclude for receipt of antibiotics with activity against any possible HAP-VAP pathogen: the exclusion could focus on recent receipt of antibiotics active against the putative pathogen. Finally, we also believe that the effect of one or two doses of non-study therapy given immediately prior to enrolment will be negligible given the severity of this syndrome, the compromised state of the patients, and the limited half-life of the relevant agents. We do agree that sponsors should seek to enrol patients who have not recently received antibacterial agents, but to balance these competing concerns we recommend that active antibiotics be permitted for up to 24 hours prior to enrolment regardless of the bacterial coverage. The analysis plan should include analyses stratified by receipt vs. non-receipt of active antibiotics during this period.
12	464-488	AstraZeneca believe that a clinical endpoint that includes 28-day All-Cause Mortality is a relevant alternative to the proposed use of 28-day All-Cause Mortality as the sole component of the primary endpoint. The proposed 28-day All-Cause Mortality endpoint is a relevant endpoint but is not the endpoint of greatest interest due to the way underlying disease will reduce the ability to measure drug effects (Wenzel & Gennings, AAC 54:4956-60, 2010). In particular, this endpoint ignores all events other than survival and thus leads to the high likelihood scenario in which a patient who requires modification of initial therapy for either lack of efficacy or adverse events will still be judged as a success of randomized therapy. Such a classification will be challenged as illogical. Conversely, a clinical endpoint that includes survival, lack of a requirement for modification of therapy, and lack of adverse events leading to discontinuation of therapy will almost certainly become the logical focus of discussion during analysis of any trial data. As this endpoint will effectively take on the force of being the primary endpoint for interpretive purposes, it meets the standard suggested by ICH E9 (Section 2.2.2): "The primary variable ('target' variable, primary endpoint) should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		primary objective of the trial." A clinical endpoint can be criticized on the basis of incorporating subjective components of physician judgement, but this critique underestimates that strength of the objective information available to the physician and the ability of the sponsor to show a linkage between physician decisions and objective improvements. Objective improvements in such parameters as PaO_2/FiO_2 ratio (Combes A et al., Crit Care Med 2007; 35:146-54) or CPIS score (Luna CM et al., Crit Care Med 2003; 31:676-82) are strongly linked to outcome and readily meet the criteria suggested for biomarkers in chronic diseases (in particular, Strength, Consistency, Specificity, Temporality, Biological Gradient, Plausibility, & Coherence; see discussion on pages 53-55 of *Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease*, National Academies Press, 2010 and Hill AB, Proceedings of the Royal Society of Medicine 58:295–300). Mortality remains an important component of the overall analysis and is an important safety check, but patients are concerned with more than survival — they also wish to avoid secondary issues such as major adverse events. Use of a clinical endpoint is the only way to ensure that the primary endpoint captures all relevant events. The consistency of the overall response, the clinical response, and the mortality response can all easily be confirmed during post-study analysis. The proposed endpoints of Clinical cure, Clinical improvement and Clinical progression appear to be different outcomes of the same endpoint. We would suggest that these endpoints (lines 476 - 488) be merged into one endpoint and defined as a cure/failure endpoint. Successful outcomes for this endpoint should be defined to include survival at 28 days and lack of need for alternative antimicrobial therapy. In summary, AstraZeneca believe that developers should have the option of 2 primary endpoints: 28-day All Cause Mortality or a Clinical endpoint that includes 28-All Cause Mortality. Each endpoint has strengths and weakness as discussed above. Sponsors should have the option to choose the endpoint that best suits their development plan. AstraZeneca believe that effect size estimates for the proposed

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		clinical outcome that includes mortality must be at least as large as that for mortality alone and thus must be substantially greater than 20%. Margin selection can thus be based on clinical reasoning as discussed below in our comments on M1 and M2.
	490	The concept of a PRO in this setting is not logical because of the patient's health status and the fact patients are often sedated at least until the patient improves. Patients with HABP-VABP are critically ill, often sedated with little ability to communicate (especially if they have VABP), and rarely in possession of their baseline mental faculties. As patients begin to improve, all of this clears (even patients with VABP can engage in logical interaction with the care providers despite their endotracheal tube), but this occurs only once they have begun to improve. Indeed, an important measure of response is the return of normal mental status (as an example of this linkage, the Glascow Coma score is part of the APACHE scoring system). It is thus not clear why the report of symptoms collected from such a patient would be preferred over the objective reports of a health care provider.
13	526-530	This section describes trials in patients with an important unmet need. It is highly probably that a single comparator will not be feasible in this patient population. Please clarify in the guidance if the agency thinks that it is reasonable to use multiple comparators in one trial to address the broadest potential range of resistant pathogens. We would propose that even this approach could be used in a randomized trial if the investigator is asked to define the preferred standard therapy prior to the randomization step. If this approach is not supported, we feel it is likely that trials capturing a representative array of these important and difficult-to-treat patients cannot be implemented in a compelling and instructive manner.
16	625-632	The MITT population in this guidance (microbiological ITT) has a different meaning than in other indications. In other indications the MITT population (modified ITT) is defined as an ITT population including patients who meet minimal disease criteria and a microbiologically confirmed population has been defined as the mMITT population. Given this has the potential to lead to confusion, we suggest that

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		consistent terminology be utilized across all indications.
	666-7 and Appendix A	The agency's efforts to estimate M1 are appreciated, but the logic behind the extensive discounting to reach M2 is unclear: the estimate starts with difference between 95% bounds, is then reduced by an arbitrary 30%, and then finally by a further arbitrary 50%. Although the final value 10% may have appeal as a round figure, values in the range of 12.5–13% are equally supportable. We would argue instead that the critical point is that these values (10% and 12.5–13%) are both well below effect size estimates of antibiotics in this syndrome, which even after discounting yield an estimated treatment effect of 20%. Therefore, selection of an NI margin should be based on clinical reasoning rather than arbitrary discounting. As such, we feel that an NI margin of 12.5–13% could be considered clinically reasonable for the reasons now discussed. Consider the case of a trial powered based on assumptions of 70% success, 10% margin within a 95% confidence interval, and 90% power. Such a study would require 442 evaluable subjects per arm. If the study results found 69.9% (=309/442) success in both arms, the resulting difference of 0% would have a 95% confidence bound of -6.0 to 6.0% and thus convincingly exclude a 10% difference between the test agent and the comparator. Looking next at the boundary case, the worse possible outcome consistent with non-inferiority for the test agent is a result of 309/442 (69.9%) vs. 292/442 (66.1%) with a difference of -3.8% and a 95% confidence bound of -10.0 to 2.3%. In this case, the likelihood of an actual difference even more substantial than -10% is precisely 2.5%. That is, there is a 97.5% likelihood that the actually difference is > -10% and a 2.5% likelihood that it is < -10%. We are thus willing to conclude non-inferiority despite the numerical trend running against the test agent. This boundary case is of great interest because it represents the worst possible scenario. If the results in this scenario are acceptable as evidence of efficacy, then so should be any case in which the difference is less extreme.

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		A simple extension of this logic follows when we observe that the guidance recommends confirmatory results be obtained from two trials. If, for example, we conduct a trial using a 12.5% margin and observe a difference with a 95% confidence bound reaching precisely -12.5%, then the likelihood that the test agent is actually 12.5% or more worse than the comparator is: • 2.5% for one trial with this actual worst case boundary condition result, and • $2.5\%^2 = 0.063\%$ for two such 12.5% margin trials Significantly, an even more useful extension of this logic is possible and permits sound clinical reasoning. Although arbitrary, the value 10% is often suggested as an attractive boundary for tolerable differences. We can thus ask the likelihood of the actual difference between test and comparator exceeding -10% for various possible margins and their corresponding worst case boundary scenarios. For a non-inferiority trial powered to a 12.5%, or even a 15% NI margin, the chances that the test drug **is truly <u>10%</u> worse than the comparator at the worse case boundary condition** (that is, the lower bound of the 95% CI just reaches –12.5% or –15%, and assuming a sample size suitable for 80% success, 90% power, and the given margin) are as follows: • 7.3% for one trial with a 12.5% margin but • $7.3\%^2 = 0.53\%$ for two trials with a 12.5% margin, • $17\%^2 = 2.8\%$ for two trials with a 15% margin, and • $7.3\% * 17\% = 1.24\%$ for the combination of one trial with a margin of 12.5% and one with a margin of 15% (this is an approach that could be used to mitigate the sample size demands for VABP discussed above by using margins of 12.5% for HABP and 15% for VABP). **Further, all of these estimates of the risk that the test agent is actually 10% or more worse than the comparator are overestimates as** they are unadjusted for the prior probability of efficacy that characterizes antibacterial agents. As the dosage regimen will have been chosen based on strong preclinical in vitro and in vivo data showing drug activity, the prior probability of efficacy in man is favourable. Demonstration of activity (and/or registration) in other

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		indications would further strengthen the prior probability of efficacy. The precise magnitude of the effect of these insights on the P value can be debated at length, but the practical consequence is that (for example), the 0.53% risk of a test agent actually being 10% worse than the comparator based on boundary case results in a pair of trials conducted with a margin of 12.5% is an upper bound on the risk: the actual value is even lower. Given that the worst case scenario for a pair of trials conducted using a **12.5% margin** produces a likelihood well under 1% that a drug found to be non-inferior by such a pair of trials would actually be **10% or more worse** than comparator, we believe that practical aspects of trial conduct should also be considered when specifying a margin. The difference between a margin of 10% and 12.5% is that the required sample size increases by slightly more than 50%. When combined with the further 2- to 3-fold increase in sample size required if the primary analysis is based on the microbiologically documented population, the resulting >3- to 4-fold impact on overall sample size is noteworthy. The requirement for very large trials has the potential for a number of negative effects: • Trial delay is a risk: Bigger trials run more slowly during which time medical practice may change, investigators may lose interest, and the trial results may become less relevant. • Drug delivery is at risk: Fewer drugs will be studied for this indication. Therefore, the high likelihood that two more moderately sized successful trials could be delivered to high quality and would also provide clear and strong statistical proof of an active compound must be weighed against the fact that there will be no drugs at all if trials are not done due to feasibility issues. Similar considerations apply to the agency's proposal to shrink the margin as the failure rate falls below 20% based on a target Odds Ratio of 1.67. Although the utility of the symmetry inherent in an odds ratio-based approach over a relative risk-based approach is appreciated, we are concerned less with theoretical application than with actual application —

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		the estimate of absolute treatment difference method is widely accepted, its use forms an integral part of the estimation of M1, and the derivation of a range for possible values of the Odds Ratio would require extensive debate. Further, the proposed Odds Ratio of 1.67 is anchored to the highly conservative 10% NI margin and the implications of following this approach have not been fully debated in public. As a specific concern, even small deviations from the target failure rate of 20% incur a substantial sample size penalty if the Odds Ratio is used to drive the margin: at a 15% failure rate, the NI margin corresponding to an Odds Ratio of 1.67 falls to 7.8%. As a result, the required sample size grows by a further 1.6-fold relative to that for a 12.5% margin and 2.6-fold relative to that for a 10% margin. When combined with a requirement to power the study for the microbiologically evaluable subset, the required sample size grows considerably. Assuming 85% success (15% failure), 90% power, and 33% microbiological evaluability, the effect of this series of requirements is to increase the total combined sample size for a two-arm trial from 1,040 (12.5% margin) to 1,624 (10% margin) to 2,670 (7.8% margin); the corresponding values at 50% microbiological evaluability are 686, 1072, and 1762. **However the growth in security of drug activity gained across this nearly 3-fold increase in sample size is limited when two trials are conducted: the worst case risk that the test drug is 10% or more worse than control is < 1% for all three scenarios.** Even with a 15% margin, the risk of such an error is 2.48% (or, < 2.5%). **The >99% likelihood that two successful trials with margins of 12.5% provide proof of an active compound is compelling. Concerns that 12.5% is "too large" or that the test agent might really be significantly worse have been addressed. Any residual concern must be weighed against the near 0% likelihood of having a drug at all for this indication if trials are not done due to feasibility issues.** Indeed, the margin can be increased to 13% (at 80% success) and still give the same <1% risk. **Finally and as noted above, the favourable prior probability of activity that characterizes all antimicrobial agents means that these risks estimates are worst case upper bounds — the actual**

Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment		
Section	**Page or Line Number**	**Comment or proposed replacement text**
		risk is lower. In summary, we conclude that a margin smaller than 12.5–13% adds a substantial burden to the development program while providing no meaningful increment in protection against the test agent being 10% or more worse than the comparator. Even a margin of 15% is associated with a worst case risk of <3.4% for studies powered for success rates of 60-85% (see Table, below).

Table. Shown below is the worst case likelihood that the test agent is 10% or more worse than the comparator if the worst case boundary scenario is observed in two identical trials powered at 90% with the given margin, the given predicted comparator success rate. **The stated worst case risk is unadjusted for the favourable prior probability of activity for an antibiotic and thus all values are overestimates of the true risk.**

The required sample size for a 33% microbiologically evaluable rate is shown in parentheses following the percentage.

Example: two trials with a margin of 13% and success rate of 85% would require 962 patients/study and lead to a risk of <0.9% if the worst case boundary condition compatible with non-inferiority were observed in both trials.

		Margin					
		15%	13%	12.5%	10%	7.8%	5.7%
Comparator success rate	90%				0.04% (1146)	0.00% (1884)	0.00% (3528)
	85%	2.5% (722)	0.9% (962)	0.5% (1040)	0.04% (1624)	0.00% (2670)	
	80%	2.9% (906)	0.9% (1206)	0.5% (1304)	0.05% (2038)		
	75%	2.4% (1062)	1.0% (1414)	0.6% (1528)	0.06% (2388)		
	70%	3.1% (1190)	1.2% (1584)	0.7% (1712)	0.06% (2676)		
	60%	3.4% (1360)	1.2% (1926)	0.7% (2084)	0.05% (3254)		

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February 23, 2011

Division of Dockets Management (HFA–305)
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Re: Comments on Docket #FDA-2010-D-0589; Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP): Developing Drugs for Treatment; 75 Federal Register 73107; November 29, 2010

Dear Sir/Madam:

These comments on the above noted Draft Guidance are submitted by the Infectious Diseases Society of America (IDSA). IDSA represents more than 9300 infectious diseases physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative bacterial infections such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and, finally, emerging infections such as the 2009 H1N1 influenza virus and bacteria containing the newly emerging New Delhi metallo-beta-lactamase (NDM-1) enzyme that makes them resistant to a broad range of antibacterial drugs. For the past decade, IDSA has raised concerns about the imbalance between the dwindling antibiotic pipeline and the significant and concomitant need for new, safe and efficacious antibacterial drugs to treat an increasing number of serious and life-threatening drug-resistant infections.

In 2004, concluding that immediate government action was essential, IDSA published its report—Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates a Public Health Crisis Brews. The report examined all aspects of the government's response to the pipeline problem and focused significantly on the need for FDA to provide clear and workable written guidance to industry about how to design antibacterial clinical trials in a way that safe and efficacious drugs could achieve FDA approval. Now, six years later, the drug pipeline and resistance problems have grown worse as more companies have withdrawn from antibiotic research and development and ever-more resistant bad bugs have spread across the United States in health care settings and communities, devastating the lives of the young and the old, the healthy and the frail. There is no doubt that the lack of clear and pragmatic FDA guidances has contributed in a significant way to the growing crisis.

IDSA welcomes this particular Draft Guidance and hopes that it can be modified to provide appropriate guidance to sponsors developing new antibiotics for these two hospital-acquired pneumonias. IDSA previously issued a position paper[1], along with the American College of Chest Physicians, American Thoracic Society and Society of Critical Care Medicine, on this topic and many of our suggestions were incorporated into the Draft Guidance (a copy of our joint position paper is enclosed). However, there are still some substantive issues that must be addressed that will ensure that clinical trials for these two indications are feasible to conduct. There are two key issues, as well as other specific points, in the Draft Guidance that IDSA believes must be addressed so that antibacterial drug development for these indications is not adversely impacted: allowance for prior antibiotic therapy prior to clinical enrollment and the use of biomarkers as an alternative to the collection of respiratory culture specimens.

Key Issues

1.) Prior antibiotics

FDA suggests that "…the prior use of antibacterial drugs effective against bacteria that cause HABP/VABP should be avoided in a non-inferiority [NI] trial because such treatments will reduce the difference between treatment arms and potentially bias conclusions about treatment effects (Lines 421-429 of the Draft Guidance)."

There are two critical deficiencies of this approach. First, requiring no antibacterial therapy in the 30 days prior to enrollment will result in infeasible studies. The great majority of patients who are hospitalized long enough to develop HABP/VABP will have been exposed to some antibiotic(s) during the hospitalization. Requiring no antibiotics within 30 days will eliminate from eligibility most patients with HABP/VABP.

Furthermore, the desire for not even a single dose of active antibacterial therapy within 24 hours of enrollment is unwarranted and will make enrollment extremely difficult. Particularly for patients with VABP, obtaining informed consent will be very difficult, as these patients will have substantial physiological derangements and will be sedated. Consent will have to be obtained from surrogate decision makers, resulting in a many hours delay in obtaining informed consent. It will not be possible to delay the administration of antibacterial therapy during that time. Furthermore, there are no data to suggest that a single dose of antibacterial therapy will affect mortality in such patients. Extrapolation from the failed daptomycin clinical trial of CABP is not appropriate. HABP/VABP is caused by far more resistant bacteria than CABP, affects far more debilitated hosts, and VABP in particular occurs in the setting of a foreign body. Furthermore, in contrast to CABP, for which most antibacterial options have a long half-life and can be administered once daily, most HABP/VABP therapies must be dosed three to four times per day due to short half-lives. Finally, even the data for the impact of single dose ceftriaxone for CABP from the daptomycin studies are based on a small number of post-hoc analyzed patients.

IDSA is aware that FDA has accepted data from sponsors where the patients enrolled in HABP/VABP trials had prior antibiotic exposure. Our understanding is that patients enrolled in prior trials frequently had received antibiotics within the previous 30 days and within the previous 24 hours. We suggest that FDA consider an analysis of the data available from

[1]Clin Infect Dis 2010 Aug 1; 51 Suppl 1:S150-70.

previous new drug applications (NDAs) to determine the impact of excluding all such patients on feasibility of future studies. For all of these reasons, FDA should allow for 24 hours of pre-study therapy, or at a minimum, one dose of a thrice or four-times daily dosed antibiotic regimen.

2.) Biomarkers for diagnosis

In the section on "Microbiologic Criteria" FDA notes "…the following topics regarding detection of bacterial pathogens should be discussed with FDA before trial initiation: (1) use of rapid diagnostic tests for bacterial pathogens or for respiratory viral pathogens; and (2) *use of biomarkers for detection of patients with bacterial disease* (Lines 359-362)."

IDSA hopes that FDA can be more explicit with respect to the use of the biomarker procalcitonin. Our enclosed position paper acknowledges that potential study sites vary in their ability to collect respiratory specimens via bronchoscopy. Further, study sites vary in their ability to perform quantitative bacteriology. So, even though quantitation of protected specimen brush, bronchoalveolar lavage, or blind aspiration specimens is desirable, it is not likely feasible in many study sites.

IDSA believes that, regardless of the type of airway culture, serum procalcitonin levels can distinguish between colonization of the airway (e.g., endotracheal tube, tracheostomy stoma) and invasive disease. Serum procalcitonin levels increase rapidly as the host innate immune system responds to invasion by bacteria. Levels rise to detectable levels within 4 hours and peak within 24 hours. Hence, if the procalcitonin level remains below 0.25 ng/ml over the first 6-8 hours of study enrollment, the patient does not have an invasive bacterial disease regardless of the culture results. The negative predictive values for procalcitonin are very high.

In short, use of procalctionin levels should facilitate clinical trials of new drugs for the treatment of VABP/HABP. Procalcitonin levels are available within one hour of receipt of serum in the laboratory. Hence, patients can be enrolled or excluded from consideration very quickly. Elevation of the procalcitonin level also strengthens the interpretation of subsequent culture results. For all of these reasons, IDSA urges FDA to place greater emphasis on the helpful role of procalcitonin levels in clinical trials of VABP/HABP.

IDSA concurs (see our position paper) that, based on currently available data, all-cause mortality is the most appropriate endpoint for a NI HABP/VABP trial. This position is based on the well established effect size of active antibacterial therapy vs. inactive (i.e., "discordant") therapy for HABP/VABP using a mortality endpoint. Unfortunately, despite active investigation of available datasets and literature, there are very few data currently in the public domain which establish an antibacterial effect size for any non-mortality, clinical endpoint. However, mortality is an insensitive endpoint (i.e., less likely to detect true differences in antibacterial efficacy than clinical endpoints), and clinical response is the preferred endpoint clinically. Therefore, IDSA urges industry and academe to conduct new studies, and re-evaluate existing datasets, to establish antibacterial effect size for clinically meaningful endpoints. Upon completion of such analyses in the future, IDSA urges FDA to move rapidly to enable NI studies of HABP/VABP to use clinical primary endpoints.

3.) Pediatric patients

IDSA believes there should be a more forceful statement about developing drugs for pediatric patients. Because the pathogens causing HABP and VABP in children are the same as those in adults, there is also a critical need for the timely availability of new agents for children. New agents that show promise against multidrug-resistant pathogens in phase 2 studies in adults and have entered into phase 3 comparative clinical trials with an acceptable safety profile and preliminary efficacy data should enter into pediatric investigations. Current timelines for drug development postpone useful data collection in the pediatric age groups by several years until the phase 3 data in adults are collected, analyzed, and presented to FDA. Initial pediatric data on pharmacokinetics and safety in several age groups already should be available to those who care for children at the time the investigational antibiotic receives approval from FDA for adult indications. Although safety data in adults may reveal toxicities that would preclude the study of agents in children, the delay in acquiring pediatric data forces those who care for children to use agents without scientific guidance on age-specific pharmacokinetics, subjecting neonates, infants, and children to possible drug toxicities that may not be seen in adults.

Our other comments with the Draft Guidance follow:

4.) Lines 268-270; as part of the clinical criteria, FDA requires "an elevated total peripheral white blood cell count (WBC) greater than 10,000/mm; or greater than 15 percent immature neutrophils (bands), regardless of the total peripheral WBC…" It is unclear to IDSA how FDA reached this threshold and it appears to be a very high number given the normal range of <7%. We would appreciate clarification on this point and why it should not be >7%, or >10% based on systemic inflammatory response syndrome (SIRS) criteria.

5.) Lines 301-303; FDA recommends using a clinical severity scoring system to define enrollment criteria to ensure a clinical trial population that has a reasonable likelihood of demonstrating mortality of approximately 20 percent or greater. IDSA believes that 20 percent is clearly too high and will lead to difficulties in both obtaining informed consent from prospective patients and enrolling a statistically valid sample in the trial. IDSA has proposed a 15-20% mortality rate target in the enclosed position paper.

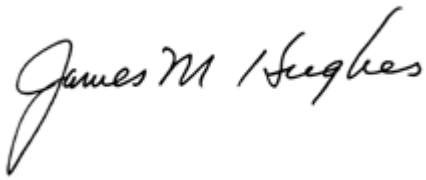
6.) Lines 342-349; FDA notes that "…colony counts of 10^3 colony forming units/ml (CFU/ml) can be considered a threshold for identifying pathologic bacteria from protected brush specimen whereas colony counts of 10^6 CFU/ml can be considered a threshold for identifying pathologic bacteria from an endotracheal tube specimen. The enclosed position paper discusses the pros and cons of this requirement for quantitation. IDSA requests clarification on whether FDA believes quantitation is an absolute requirement or if there are circumstances when it isn't required.

7.) Lines 410-419; FDA suggests that the choice of a comparator drug should be one "…that is FDA-approved for treatment of "nosocomial pneumonia" or "HABP/VABP" or is FDA-approved for the treatment of "lower respiratory tract infection" with the appropriate antibacterial spectrum for pathogens encountered in HABP/VABP." IDSA notes that great care must be taken here as many drugs that were standard treatments in the past are no longer useful because of high resistance rates and likely not to be a good drug of choice for a comparator. Furthermore, resistance rates vary widely across intensive care units, and it is necessary for a protocol to have sufficient flexibility to enable appropriate, active antibacterial therapy to be used as comparators across sites.

8.) With respect to statements indicating that patient reported outcomes (PROs) are appropriate, these are not realistic for HABP/VABP. Patients with HABP/VABP have severe physiological derangements. VABP patients are sedated. It is not feasible to ask such patients to complete PROs in the midst of their illness.

IDSA hopes that these comments are useful to FDA as the agency moves forward to finalize this Draft Guidance. We would be pleased to provide clarification of any of the points raised in this letter.

Sincerely,



James M. Hughes, MD, FIDSA
President

Enclosure: IDSA/ACCP/ATS/SCCM 2010 position paper on HABP/VABP clinical trials

SUPPLEMENT ARTICLE POSITION PAPER

Recommended Design Features of Future Clinical Trials of Antibacterial Agents for Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

Brad Spellberg[1,2] and George Talbot,[3] for the Infectious Diseases Society of America, American College of Chest Physicians, American Thoracic Society, and Society of Critical Care Medicine

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EXECUTIVE SUMMARY

The efficacy of new antibacterial agents for the treatment of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) has typically been compared with that of established antibacterial agents in noninferiority clinical trials. However, the US Food and Drug Administration (FDA) has reevaluated the appropriateness of noninferiority trial designs for a variety of diseases, including HAP and VAP. The resulting regulatory uncertainty regarding appropriate trial design is an important barrier to the development of new antibacterial agents.

After a recent, successful workshop focusing on community-acquired pneumonia (CAP) that was cosponsored by the Infectious Diseases Society of America (IDSA) and the FDA, the FDA released a draft guidance on the design of trials for community-acquired bacterial pneumonia (CABP) that has greatly clarified regulatory expectations for such studies. In the guidance, the FDA specifically referred to the disease entity as CABP rather than CAP to emphasize the critical need to establish a bacterial etiology of infection for noninferiority clinical trials of the disease.

After the successful workshop on CABP, the FDA, the IDSA, the American Thoracic Society (ATS), the Society of Critical Care Medicine (SCCM), and the American College of Chest Physicians (ACCP) jointly sponsored a follow-up workshop focusing on hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) from 31 March through 1 April 2009. In accordance with the precedents established by the FDA guidance on CABP, the follow-up workshop focused specifically on HABP and VABP (as opposed to HAP and VAP) to underscore the need to establish a microbiological diagnosis during clinical trials of antibacterial agents for treatment of these diseases.

The workshop provided a forum for scientific discussion to clarify appropriate design elements of clinical trials of HABP and/or VABP. This position paper reflects the conclusions and suggestions of the societies that resulted from the workshop. For topics on which clear consensus could not be achieved or on which strongly held dissenting opinion was evident, alternative design features are presented.

Data reviewed at the workshop and summarized in this supplement and position paper make clear that there is an unequivocal and substantial treatment effect of antibiotic therapy for HABP and VABP. Thus, noninferiority trials are appropriate for the study of experimental antibacterial agents for the treatment of HABP and/or VABP. On the basis of the reviewed data, the societies support the following design features for registration studies of HABP and/or VABP.

1. On the basis of data available to date, acceptable trial designs include at least one of the following options:

a. Noninferiority trials using all-cause mortality as the primary efficacy end point at 30 days in the microbiological modified intention-to-treat (mMITT) population (ie, patients with culture-confirmed HABP and/or VABP who have received at least 1 dose of study drug), using a 10% (absolute) margin of noninferiority.

b. Superiority trials for the study of combination therapy with an experimental agent plus currently available antibacterial therapy, compared with currently available antibacterial therapy plus placebo. Superiority trials are also appropriate for the study of HABP and/or VABP caused by extensively drug-resistant (XDR) or pan–drug-resistant gram-negative pathogens.

c. Carefully conducted, historical controlled trials may also be acceptable for the study of HABP and/or VABP caused by XDR or pan–drug-resistant gram-neg-

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ative pathogens. The societies emphasize that further discussion is urgently needed regarding appropriate design features for superiority and historically controlled trials of HABP and/or VABP caused by XDR or pan–drug-resistant gram-negative pathogens.

2. Recommendation for use of a mortality-only primary efficacy end point for noninferiority studies of antibacterial agents for HABP and/or VABP is based on the limited available data with which to estimate the magnitude of benefit of effective antibacterial agents, compared with initially inactive therapy, for clinical end points. Nevertheless, the societies strongly emphasize that limiting trials to a mortality-only primary efficacy end point is not consistent with standard clinical practice. Because physicians routinely assess response to antibacterial therapy for HABP and/or VABP by evaluating clinical biomarkers (eg, resolution of fever, normalization of white blood cell [WBC] count, improvement in oxygenation, and ability to extubate patients), results of noninferiority trials using a mortality-only primary efficacy end point may not extrapolate well to postapproval use of antibacterial agents. Therefore, the societies strongly encourage additional research to allow the use of clinical primary end points in future noninferiority trials of HABP and/or VABP. Specifically, analysis of the impact of discordant antibacterial therapy should allow documentation of the magnitude of treatment effect on these clinical end points. When results of such analyses become available, the use of composite mortality and clinical primary end points should be adopted as rapidly as possible, to make the trials relevant to subsequent clinical use of the studied drugs.

3. Use of either of the following 2 options for adjudication of receipt of salvage antibacterial agents after randomization as indicating study failure or not:

a. Adjudication of success or failure on the basis of all-cause mortality on an ITT basis, without considering the use of salvage antibacterial agents. In this scenario, the statistical analysis plan must account for the use of salvage antibacterial agents (eg, by comparing use in both arms).

b. Adjudication of success or failure on the basis of all-cause mortality but with consideration of receipt of salvage antibacterial therapy also indicating study failure. In this scenario, double-blinding of the study (ie, blinding of patient and investigator deciding to initiate salvage therapy) is necessary to minimize bias in end point adjudication, and consideration should be given to prespecifying objective criteria triggering the initiation of nonstudy salvage therapy.

4. Clinical end points can be included as superiority components in a hierarchical primary efficacy end point, after first establishing noninferiority for all-cause mortality. As mentioned, if more data become available in the future to enable determination of the effect size of active versus inactive antibacterial therapy on clinical end points that provide clear patient benefit, composite primary efficacy end points combining all-cause mortality with clinical cure rates could then be justified for noninferiority studies.

5. Study enrollment should be based on standard clinical and radiographic criteria, which serve to increase the pretest probability of a subsequent positive respiratory culture result.

6. A severity-of-illness scoring system should be incorporated as part of the enrollment criteria to ensure an adequately ill population of patients in support of the justification of the noninferiority margin (ie, targeting 15%–20% all-cause mortality in the control arm). Enrollment of only intensive care unit (ICU) patients is another means to enrich the population for an appropriate level of disease severity.

7. Microbiological confirmation of infection by deep lower respiratory tract culture is required for inclusion in the mMITT population, and enrolled patients whose culture results are subsequently found to be negative should be deemed to be nonevaluable for the primary efficacy end point (but included in the safety ITT population).

8. For HABP and/or VABP trials, the acceptable method by which lower respiratory tract samples should be obtained was the subject of considerable controversy. Many workshop participants believed that samples obtained for quantitative cultures with use of bronchoscopy were strongly preferred. If not feasible, mini-bronchoalveolar lavage (BAL) fluid or carefully obtained deep-suction endotracheal aspirate specimens (for patients with VABP) or purulent expectorated sputum specimens (for patients with HABP) could be considered as adequate. Other means to obtain microbiological confirmation of infection include positive pleural fluid culture results, positive blood culture results in the context of clinical and radiographic evidence of HABP and/or VABP, and urinary antigen testing. The societies underscore the need for advances in molecular diagnostic testing to confirm the microbiological etiology of HABP and/or VABP, and when such technologies become available and are validated, they could be used for this purpose in addition to cultures in clinical trials.

9. Patients with HABP and/or VABP may be enrolled if enabling data are available to support a rational dose selection and expectation of similar microbiology for all enrolled patients and if microbiological confirmation of infection is available from all evaluable patients.

10. Selection of adequate comparator antibacterial treatment regimens (including dose and duration of therapy) and adjunctive antibacterial therapy for the experimental arm should be based on ATS and IDSA guidelines of standard of care for HABP and VABP. Primary principles used to select specific comparator antibiotics include (1) local microbiology data at enrolling sites; (2) if possible, avoidance of overlapping spectra of activity for adjunctive therapy and the experimental drug; (3) double coverage of certain gram-negative bacilli should be included when indicated by ATS and IDSA guidelines

(even if activity overlaps), and a preplanned analysis should be conducted to evaluate the frequency of use of double therapy for gram-negative bacilli in the comparator versus control arms; and (4) antibacterial coverage in the control arm and adjunctive therapy in the experimental arm should be narrowed as rapidly and thoroughly as possible after culture results are available.

11. Study participants should be stratified during enrollment on the basis of risk of multidrug-resistant (MDR) or XDR pathogens, HABP or VABP (if patients with both are enrolled), and severity of illness.

12. HABP and/or VABP studies should be double-blinded (ie, to patient and observer) at a minimum. Blinding of clinical care team and end point adjudicators and use of a double-dummy infusion design are desirable if feasible.

13. Care should be taken in selecting high-quality study sites, regardless of geographic location, to ensure adequacy of study conduct and data abstraction.

14. The societies strongly endorse the need for creation and use of a clinical trials network that would enable high-quality studies of HABP and/or VABP to be conducted.

The current uncertainty in acceptable designs for clinical trials of HABP and/or VABP is contributing to disincentives in the discovery and development of new drugs for these diseases. After a related workshop on CAP, the FDA released a guidance document that provided clear directions for conduct of trials of CABP. The societies desire similar approval and dissemination of clear and scientifically and clinically defensible guidelines for future clinical trials of new antibacterial agents for the treatment of HABP and VABP.

INTRODUCTION

Nosocomial pneumonia, including HAP and VAP, is the second leading type of nosocomial infection and the leading cause of death from nosocomial infection in the United States [1–3]. An estimated 300,000 HAP and VAP infections occur per year in the United States, and the mortality rate among patients with HAP and/or VAP is ⩾20% despite treatment [3, 4]. Furthermore, increasing antibacterial resistance because of the increasing incidence of MDR, XDR, or truly pan–drug-resistant gram-negative bacilli continues to increase the mortality associated with these infections [5–16].

Unfortunately, at the same time that increasing drug resistance has created a crucial need to develop new treatments, the development of new antibacterial agents has been decreasing dramatically [17, 18]. Uncertainty about regulatory requirements for the appropriate design of clinical trials testing the efficacy of antibacterial agents is a major barrier to research and development and likely has contributed to the decrease in availability of new antibacterial agents [17]. In January 2008, the IDSA and the FDA jointly convened a workshop to elucidate an appropriate clinical trial design for CAP [19]. The workshop allowed experts from academia, industry, and the FDA to share pertinent knowledge about clinical trials for CAP. On the basis of the scientific and regulatory discussions at the workshop, the IDSA published a position paper synthesizing the crucial elements of appropriate trial design for CAP [20]. Subsequently, the FDA released a draft guidance on the design of trials for CABP [21], which has greatly clarified regulatory expectations for such studies. In the guidance document, the FDA specifically referred to the disease entity as CABP rather than CAP, to emphasize the crucial need to establish a bacterial etiology of infection for noninferiority clinical trials of the disease.

After the successful workshop on CABP, the FDA, the IDSA, the ATS, SCCM, and ACCP jointly sponsored a follow-up workshop focusing on HABP and VABP from 31 March through 1 April 2009. In accordance with the precedents established by the FDA guidance on CABP, the follow-up workshop focused specifically on HABP and VABP (as opposed to HAP and VAP) to underscore the need to establish a microbiological diagnosis during clinical trials of antibacterial agents for treatment of these diseases.

This position paper is based on the data presented, discussions held, and opinions expressed at the HABP and/or VABP workshop and an ongoing dialogue subsequent to the workshop. Conclusions and suggestions presented in this document are those of the societies. There is no intent to represent the views of industry or the FDA. The societies' goal is to consider the data and represent the best interests of patients by providing clarity to clinical investigators, clinicians, the pharmaceutical industry, and regulatory officials regarding appropriate clinical trial design for the study of investigational antibacterial agents in the treatment of HABP and VABP. For topics on which a clear consensus could not be achieved or on which strongly held dissenting opinion was evident, alternative design features are presented.

Consideration is given to 8 specific aspects of clinical trial design for HABP and/or VABP: (1) justification for a noninferiority versus a superiority hypothesis; (2) primary and secondary end point evaluations and the patient populations in which they should be assessed; (3) enrollment criteria including microbiological diagnostic methodologies; (4) advisability and difficulties with study of HABP and VABP in the same clinical trial rather than in separate trials; (5) appropriate standard comparator and adjunctive therapy; (6) factors by which enrollment should be stratified; (7) trial integrity issues, including blinding, use of international sites, and the desirability of a clinical trials network; and (8) core components of a HABP and/or VABP clinical trials program.

JUSTIFICATION FOR A NONINFERIORITY VERSUS A SUPERIORITY HYPOTHESIS

Can a noninferiority trial design for HABP and/or VABP be justified?

The inherent difficulty of conducting clinical trials to determine whether new antibacterial agents are superior in efficacy, compared with approved agents has been discussed elsewhere [20, 22]. In brief, new antibacterial agents are more likely to achieve superior efficacy than are comparator drugs when used to treat infections caused by organisms resistant to the comparator drugs. However, patients with infections caused by organisms resistant to standard comparator drugs are excluded from enrollment in clinical trials. Therefore, new antibacterial agents typically cannot be tested in the very patients in whom they are likely to achieve superior efficacy, compared with comparator drugs. It is not surprising, therefore, that all recent trials of antibacterial agents for HABP and/or VABP have been noninferiority studies [23, 24]. Situations exist in which superiority trials of antibacterial agents for HABP and/or VABP would be both feasible and desirable (discussed further below); however, in most instances, clinical trials of new antibacterial agents for the treatment of HABP and/or VABP are likely to be noninferiority trials.

According to guidance documents from the International Congress on Harmonization (ICH) [25, 26] and the FDA [27], noninferiority trials are appropriate only when a comparator drug has been established previously to be superior in efficacy to placebo or no therapy for the disease in question (ie, the historical evidence of sensitivity to drug effect standard). Furthermore, the clinical contexts in which the efficacy of the comparator drug was previously established must be relevant to the planned noninferiority trial (ie, the constancy assumption standard). Unfortunately, as is true of other severe infections [20, 22], no placebo-controlled studies of antibacterial agents for the treatment of HABP and/or VABP are available, because antibacterial agents became available in an era before the widespread use of placebo-controlled studies. Furthermore, active antibacterial agents were already being used to treat HABP and/or VABP before the FDA designation of these infections as antibiotic indications. The lack of placebo-controlled studies complicates justification of noninferiority margins for new antibacterial agents for the treatment of HABP and/or VABP.

To evaluate evidence about the acceptability of a noninferiority design for clinical trials of HABP and/or VABP, Sorbello et al [24] from the FDA conducted an extensive search of the literature from the period 1969–2008. They focused on studies of delayed initiation of effective antibacterial therapy for HABP and/or VABP as a proxy for placebo or no therapy data. A substantial number of studies have evaluated the impact of delayed initiation of effective therapy for HABP and/or VABP [28–39]. Sorbello et al [24] reviewed the subset of these studies that most closely reflected the patient age and severity of illness in recent registration studies of antibacterial agents for the treatment of HABP and/or VABP. Their analysis revealed a ⩾29% absolute reduction in mortality among patients with HABP and/or VABP treated with active antibacterial therapy (ie, therapy to which the etiological organism was susceptible in vitro), compared with when initial antibacterial therapy was inactive for the organism causing the infection (ie, therapy to which the etiological organism was resistant in vitro).

The primary limitations of this estimate are the reliance on meta-analysis of nonrandomized studies of delayed initiation of active therapy and the absence of placebo-controlled trials [24]. Nevertheless, Sorbello et al [24] used conservative random-effects methods to analyze the data. Furthermore, the estimate of antibacterial efficacy based on delayed initiation of effective antibacterial therapy is likely to be inherently conservative, because the duration of delay in initiation of effective therapy in the analyzed studies was typically 1–3 days. It seems probable that the mortality rate associated with HABP and/or VABP episodes that remained untreated during the entire duration of illness would be substantially higher, compared with the mortality associated with a <72 h delay in initiation of effective antibacterial therapy.

A specific concern about the analysis discussed at the workshop was that delayed initiation of effective therapy might be more likely to occur in more severely ill patients with a higher mortality rate due to their underlying diseases, compared with patients who received initially effective antibacterial therapy. However, initial discordant therapy is most likely to occur when patients are infected with MDR pathogens. As indicated in the consensus ATS and IDSA guidelines on the management of nosocomial pneumonia [40] and as summarized in the current supplement [41–44], baseline disease severity does not correlate with risk that HABP and/or VABP is caused by MDR pathogens. Instead, the factors associated with infection due to MDR pathogens and, thus, associated with increased risk of receipt of initially ineffective antibacterial therapy include prior exposure to antibiotics and exposure to environments in which MDR organisms are present (discussed further below).

The reliability of the aforementioned estimate of efficacy of antibacterial therapy for HABP and/or VABP, compared with placebo or no therapy, is substantiated by other data. For example, in accordance with the analysis by Sorbello et al [24], an independent analysis of the literature on delayed initiation of effective antibacterial therapy for HABP and/or VABP included the results of all identified studies of delayed initiation of effective therapy [45]. Thus, this second evaluation serves as a useful sensitivity analysis of the estimate of antibacterial efficacy derived by Sorbello et al [24], based on their more focused analysis. The broader, random-effects meta-analysis found a ⩾33% reduction in mortality when initial antibacterial therapy was effective, compared with when it was ineffective [45]—a result similar to that generated by the more focused meta-analysis of Sorbello et al [24]. The concordance of the broader analysis,

which incorporated more studies with more variation in underlying disease severity and patient age, provides reassuring evidence that the estimate of the mortality benefit of effective antibacterial therapy for HABP and VABP is robust.

Additional evidence that the estimate of antibacterial efficacy for nosocomial pneumonia is robust is provided by natural history studies of untreated pseudomonal nosocomial pneumonia [46, 47]. These studies found that ~60% of such patients died without therapy, similar to the meta-analytic estimates of mortality related to delayed initiation of antibacterial therapy in more recent studies.

Historical literature identified after the workshop lends further credence to the substantial efficacy of antibacterial therapy for nosocomial pneumonia. For example, in 1952, Kassowitz and Muscato [48] published data from >74,000 admissions over 20 years to a pediatric hospital to determine the efficacy of antibacterial therapy for the treatment of pulmonary infections. The period analyzed spanned the pre- and immediate postantibiotic era. With a specific focus on the subset of patients who developed nosocomial pneumonia (termed "secondary pneumonia"), the mortality rate was >50% every year before 1936. In 1936, immediately after the availability of sulfonamide therapy, mortality rates decreased to ~20%, reflecting an absolute 30% reduction in mortality resulting from sulfonamide therapy; other studies showed that sulfonamide therapy was substantially less effective than penicillin therapy [20]. Furthermore, Glew et al [49] evaluated the impact of effective versus ineffective therapy on mortality in 25 patients with pneumonia caused by *Acinetobacter* species. The mortality associated with pneumonia treated with effective antibiotics was 14%, compared with an 82% mortality rate among patients treated with ineffective antibiotics. Finally, the magnitude of efficacy of antibiotics for the treatment of HABP and/or VABP appeared to be similar to the magnitude of efficacy of antibiotics for treatment of the most severe forms of CAP reviewed at the previous workshop and in subsequent proceedings [20, 50, 51].

These collective data, derived from multiple independent sources, provide considerable, robust evidence of the accuracy of the estimate of the minimal effect size of antibacterial therapy for HABP and/or VABP. A conservative estimate is that effective antibacterial therapy results in a 30% absolute reduction in mortality associated with HABP and/or VABP, compared with placebo or no therapy. The large effect size and the robustness of the analyses supporting the estimate clearly indicate that noninferiority studies are acceptable for antibacterial agents for the treatment of HABP and/or VABP.

Active controlled superiority studies of HABP and/or VABP. As mentioned, establishment of superior efficacy of a new antibacterial agent is made difficult by study exclusion of patients infected by organisms resistant to the study comparator drug(s). Furthermore, placebo-controlled superiority trials of HABP and/or VABP cannot be conducted because of the high mortality associated with the disease and the availability of effective antibacterial therapy for most cases. However, there are specific circumstances for the treatment of HABP and/or VABP in which superiority of a new agent should be feasible to achieve and in which superiority trials may be preferred to a noninferiority design.

The marked increase in the incidence of HABP and/or VABP caused by XDR or truly pan–drug-resistant gram-negative bacilli has created a situation in which superiority, compared with relatively ineffective standard therapy, can be tested ethically and appropriately in a clinical trial. When HABP and/or VABP is caused by organisms resistant to virtually all other agents, the standard of care is to treat the infection with the antibacterial agents to which the pathogen remains susceptible (eg, colistin), because no other therapy is available for such infections. Because of the lack of alternative therapy and the low efficacy of current standard of care in this context [52–58], a superiority trial testing the efficacy of a promising experimental antibacterial agent, compared with standard therapy, for HABP and/or VABP caused by XDR gram-negative bacilli would be ethical, appropriate, feasible to have approved by institutional review boards, and desirable to advance the science and clinical therapy of these infections.

Superiority testing of antibacterial agents for the treatment of HABP and/or VABP would also be desirable in the context of adjunctive therapy to improve outcomes of infection. Such a study would compare standard-of-care therapy plus the novel adjunctive therapy with standard-of-care therapy plus placebo. The comparator arm should include placebo to enable blinding of the study. The addition of a new antibacterial agent to an existing regimen to improve outcome of infection can only be tested in a superiority study, because achievement of noninferiority in that context would not constitute evidence of efficacy of the new agent. Some examples of new agents that would be appropriate for testing in the context of adjunctive therapy plus available adjunctive therapy are (1) inhalational agents targeting MDR or XDR organisms, (2) new systemic agents with spectra of activity focusing on certain MDR or XDR organisms, or (3) immunomodulatory adjunctive therapy.

Precise design features of superiority studies in this context were not discussed extensively at the workshop. Important issues to consider in designing such studies are (1) whether patients should be enrolled during the empirical therapy stage, with narrowing of the evaluable population after microbiological confirmation, or after microbiological confirmation of the MDR and/or XDR organism causing the infection; (2) the acceptability of a standard-of-care control regimen to the FDA and other regulators, because of the innate variability that can be found in such approaches and the need to have a well-justified rationale for selection of the com-

parator regimen; and (3) the complexities of blinding for such a superiority study. Because of these questions, the societies recommend that a follow-up workshop be convened to discuss the design and conduct of registration studies of agents active against MDR and/or XDR pathogens.

Historically controlled superiority studies of HABP and/or VABP caused by XDR or pan–drug-resistant organisms. Because of the lack of efficacy of most antibacterial agents for HABP and/or VABP caused by XDR or pan–drug-resistant organisms, consideration should be given to the potential use of historical controls in a clinical trial of a new agent with activity against such organisms. The possibility of historically controlled superiority studies in this context was not discussed on the record at the workshop but has been the focus of subsequent dialogue related to the workshop and is explicitly mentioned as a possibility in a relevant ICH guidance [25].

Specifically, the ICH E10 guidance indicates that, "in unusual cases … it may be possible to use a similar group of patients previously studied as a historical control" for clinical trials [59, p 7]. The guidance emphasizes that, if a historical control group is to be used for a clinical trial, the control subjects should be selected from a "well-documented population of patients … on the basis of particular characteristics that make them similar to the treatment group" [60, p 30]. The guidance continues, "The inability to control bias restricts use of the [historical] control design to situations in which the effect of treatment is dramatic and the usual course of the disease highly predictable. In addition, use of [historical] controls should be limited to cases in which the end points are objective and the impact of baseline and treatment variables on the end point is well-characterized" [60, p 30].

In accordance with the ICH E10 guidance, the reliable, high mortality rate associated with untreated or ineffectively treated HABP and/or VABP enables potential use of historical controls for a clinical trial of an experimental antibacterial agent against HABP and/or VABP caused by XDR or pan–drug-resistant gram-negative bacilli. The ICH E10 guidance specifies criteria to be incorporated in the historical controls to elevate the rigor of the study to the level necessary for registration clinical trials. The guidance specifies that "[historically] controlled trials are most likely to be persuasive when the study end point is objective, when the outcome on treatment is markedly different from that of the external control and a high level of statistical significance for the treatment-control comparison is attained, when the covariates influencing outcome of the disease are well characterized, and when the control closely resembles the study group in all known relevant baseline, treatment (other than study drug), and observational variables" [61, p 32].

Prospective establishment of a robust and well-characterized observational cohort of patients with HABP and/or VABP caused by XDR or pan–drug-resistant gram-negative bacilli could fulfill the rigorous criteria specified in the ICH E10 guidance on historically controlled studies. For example, such a database could be constructed by enrolling the prospective observational cohort that will serve as the historical control proximate to the planned initiation of the experimental arm of the study, such that the patients ultimately enrolled in the experimental arm are demonstrably similar to those in the observational cohort serving as the historical control subjects. Furthermore, prespecified analysis of baseline patient characteristics and covariates that predict mortality could be planned between the historical control subjects and the experimental arm to validate the similarity of the populations. The experimental arm most likely would consist of open-label administration of the experimental drug to the second cohort. The prespecified primary efficacy outcome of the study would be all-cause mortality as the most objective measure possible, with the experimental arm tested for superiority against the historical control subjects.

The societies emphasize that active dialogue (eg, by means of a follow-up workshop) regarding clinical trial designs for the study of infections caused by organisms for which there is limited (or no) effective antibacterial therapy would be greatly beneficial. The possibility of historically controlled studies in this context should be a focus of discussion.

PRIMARY AND SECONDARY END POINT EVALUATIONS AND THE PATIENT POPULATIONS IN WHICH THEY SHOULD BE ASSESSED

Mortality as the primary efficacy end point for a noninferiority study. As discussed above, the data supporting a substantial treatment effect size of initial effective, compared with ineffective, antibacterial therapy for HABP and/or VABP are based entirely on estimates of all-cause mortality. On the basis of the precedent established for CABP [17], a decrease in survival benefit of >10% with effective antibacterial therapy for the treatment of HABP and/or VABP is clinically unacceptable. Because of the substantial treatment effect of active antibacterial therapy (ie, absolute reduction in mortality of ⩾30%), a 10% absolute margin of noninferiority can be justified and is appropriate for all-cause mortality as a primary efficacy end point in a noninferiority clinical trial of antibacterial therapy for HABP and/or VABP.

Multiple speakers at the workshop emphasized that adjudication of attributable mortality is problematic and frequently inaccurate for HABP and/or VABP, in the context of which underlying diseases and comorbidities are common. Therefore, the majority of workshop participants believed that all-cause mortality should be evaluated in lieu of attributable mortality. However, some workshop members believed that attributable mortality was a more clinically relevant end point.

The optimal timing in the course of a

HABP and/or VABP registration trial at which mortality is evaluated was the subject of considerable discussion among the workshop panel members. The primary advantage of an earlier (eg, 14 days) analysis of mortality is the potential to eliminate from analysis late deaths related primarily to progression of underlying disease or to development of intercurrent events unrelated to the original pneumonia. In addition, the pathogenesis of HABP and/or VABP is primarily an aspiration event, and patients could continue to aspirate and, therefore, be at risk of early recurrence not because of failure of the initial course of therapy. However, the consensus of the workshop panel was that analysis of all-cause mortality at a later time (ie, 28–30 days) was more appropriate for trials of HABP and/or VABP for several reasons. First, recent registration trials that have formed the basis for the determination of the magnitude of antibiotic efficacy for the disease have shown a continual increase in mortality over the entire 30-day period after study enrollment. Second, modern critical care can artificially prolong the time to death; therefore, the time of death may vary by several weeks, based on decisions about the duration of supportive care before withdrawal of care from moribund patients. With an earlier analysis for all-cause mortality, there is a risk of obscuring true differences in mortality rates because of continued life support through the period of the earlier analysis despite eventual withdrawal of care. Finally, it was emphasized that HABP and/or VABP can result in initiation of complex physiological and inflammatory cascades (eg, systemic inflammatory response syndrome and acute respiratory distress syndrome) that continue to affect mortality among patients even after resolution of active infection. Therefore, changes in mortality occurring after 14 days may reflect a true modulatory effect of an experimental drug relative to control drugs on HABP- and/or VABP-induced physiological or inflammatory cascades. Nevertheless, some workshop participants favored a shorter, 14-day mortality end point, which could potentially eliminate confounding causes of death at later times.

Initiation of salvage antibacterial therapy after randomization. With the assumption that a noninferiority trial design would use a mortality end point, vigorous debate at the workshop revolved around how to adjudicate the outcome of a patient who is experiencing therapy failure clinically and for whom salvage antibacterial agents were administered after randomization. Of note, this concern is distinct from that raised by use of adjunctive antibacterial therapy during study drug treatment that has overlapping activity with the study medication or that raised by concomitant therapy administered for a distant site infection (both discussed below).

Many of the panel members at the workshop believed that a patient given salvage antibacterial agents after randomization should be considered as having experienced clinical failure from the perspective of the primary efficacy end point. In contrast, others argued that adjudicating such a patient as experiencing clinical failure introduced subjectivity to the end point analysis and would run the risk of invalidating the statistical justification of the noninferiority margin, which is based on all-cause mortality data, without consideration of subjective determination of disease progression or clinical failure. The latter panel members argued instead that patients receiving salvage therapy should be adjudicated on the basis of all-cause mortality on a strict ITT basis, irrespective of the use of salvage therapy.

The major advantage of not adjudicating a patient receiving salvage antibacterial therapy who experiences clinical failure is the maintenance of a pure all-cause mortality primary efficacy end point. A strict all-cause mortality end point is totally objective, which somewhat mitigates the potential for a non–double-blinded study design to introduce unmeasured bias in end point adjudication. Therefore, if a double-blinded study design is problematic because of characteristics of the study or comparator drugs (eg, different dose administration schedules and colored intravenous solutions), a primary outcome measure of all-cause mortality based on initial randomization, irrespective of use of salvage antibacterial therapy, could be a useful mechanism to mitigate bias.

The problem of not adjudicating use of salvage antibacterial therapy as failure arises if such use is not balanced between the 2 study arms. An extreme example of this point was discussed at the workshop. If noninferiority were achieved for the primary efficacy end point of all-cause mortality but 90% of the salvage antibacterial agent use was in the experimental arm, it would be difficult to accept a conclusion that the experimental drug was not unacceptably worse than the comparator. During the workshop, representatives from the FDA agreed that such a study result would raise considerable concern during regulatory review.

The ICH E10 guidance document emphasizes that "the determination of the margin in a noninferiority trial is based on both statistical reasoning and clinical judgment" [25, p 15]. In this context, adjudication of salvage antibacterial therapy as equivalent to death for analysis creates problems with statistical justification of the noninferiority margin for the study. On the other hand, use of salvage antibacterial therapy is an indicator of clinical failure of the therapy to which that patient was assigned. Clinically, it would not be acceptable to use a drug that was clearly inferior in efficacy, simply because effective salvage therapy was available for the patient after progression during receipt of the previous therapy. The fact that the decision to add salvage antibacterial therapy is not strictly objective creates concerns about statistical bias in end point analysis, but it is consistent with standard clinical practice. Therefore, not adjudicating the use of salvage therapy as a failure runs the risk of making the results of the clinical trial irrelevant to clinical practice.

Reconciliation of these competing sta-

tistical and clinical concerns is problematic to achieve. Indeed, more so than any other issue discussed at the workshop, the decision regarding how to adjudicate patients who receive salvage antibacterial therapy after randomization cannot be made clearly on the basis of ICH guidance, because either position can be justified by either statistical or clinical reasoning. In light of the equipoise on this issue, it is prudent to consider both options as acceptable if certain measures are taken to protect the integrity of the study and its interpretation.

On the basis of the aforementioned considerations, the societies agreed to an acceptable compromise on this issue. Option 1 is adjudication on a strict ITT basis of all-cause mortality, without consideration of postrandomization salvage therapy to indicate failure. This method is statistically advantageous, but runs the risk of making the trial results less relevant to standard clinical practice. This approach is clearly preferred for studies that cannot be double-blinded. If this strategy is used, the statistical analysis plan should account for the impact of institution of salvage therapy by other analyses (eg, by prospectively planned comparison of use in both arms).

The second option is adjudication of failure on the basis of all-cause mortality or the postrandomization addition of salvage therapy. This method may be statistically less desirable, but it is more clinically relevant than the first option. If this strategy is used, both the patient and the observer (ie, the assessor who determines that salvage therapy is necessary) must be blinded. If feasible by study design (see discussion on blinding below), blinding of other study personnel and clinical teams should be strongly considered. Furthermore, irrespective of study blinding, prospectively defined objective criteria should be included in the protocol that indicate the factors that should trigger use of salvage antibacterial therapy. With use of either option, the protocol should specify the reason that such nonstudy therapy was used, so that a prospective analysis of the factors driving the nonstudy therapy in both arms can be conducted.

Impact of use of other nonstudy therapy on end point assessment. Because of the severity of illness and frequent comorbidities in patients with HABP and/or VABP, use of other antibacterial and nonantibacterial therapies is frequently required for appropriate clinical management. Standardization of nonantibacterial therapies is an important feature of study design, albeit challenging because of differences in standards of care nationally and internationally. Nonetheless, standard-of-care therapy must be delivered in both the experimental and the control arms of a HABP and/or VABP study [41]. Such therapy includes timely initiation of antibacterial therapy, deescalation of therapy on the basis of microbiology, proper dosages and duration of antibacterial therapy, and proper mechanical ventilation management for patients with VABP.

Adjunctive antibacterial therapy also presents challenges [62, 63]. In many patients, effective therapy of HABP and/or VABP requires >1 agent to achieve the necessary spectrum of activity (discussed further below). Another difficulty arises when adjunctive therapy is required for a distant site infection, such as a urinary tract infection, as opposed to the primary indication of HABP and/or VABP. Because of the frequency with which intercurrent infections unrelated to pneumonia occur in patients with HABP and/or VABP, exclusion of all such patients from the primary analysis population is impractical. However, the spectrum of activity and duration of adjunctive antibacterial therapy for infections unrelated to pneumonia should be kept as narrow as possible. The frequency of such antibacterial use in each study arm should be assessed, and if a difference is observed, a sensitivity analysis should be performed to elucidate the impact of such therapy on the primary end point.

Other clinical end points. The societies strongly and unanimously believe that it is essential to incorporate clinical components in the primary efficacy end point to make HABP and/or VABP clinical trials relevant to clinical practice. Unfortunately, little historical evidence was available to serve as a basis for justifying a noninferiority margin for any end point other than all-cause mortality. Two datasets available at the workshop that could enable an estimate of antibiotic efficacy for clinical end points focused on defervescence and resolution of hypoxemia. Specifically, Vidaur et al [64] published Kaplan-Meier curves of time to resolution of fever in patients with pseudomonal VABP treated initially with appropriate versus inappropriate antibacterial therapy. The effect size of defervescence in the context of initial appropriate versus inappropriate antibacterial therapy was substantial, both from a time-to-event perspective (ie, comparing areas under the curves) and by dichotomous analysis of defervescence at specified times. For example, on day 7, the proportion of febrile patients in the initially ineffective therapy group was 50% higher on an absolute basis than the proportion of febrile patients in the effective therapy group (~65% vs ~15%). This magnitude of benefit of effective antibacterial therapy on defervescence in the context of VABP is similar to that previously summarized for CABP [20].

The relevance and complexity of using defervescence as a marker for clinical response to therapy has been discussed previously in the context of end points for CABP [20]. Furthermore, duration of fever has been shown to be important as a marker of resolution of VABP. For example, using data from a recent, large, randomized, controlled trial of patients with VABP, Shorr et al [65] reported that, by multivariable analysis, persistence of fever was the only factor associated with clinical failure in patients who survived infection. Therefore, defervescence is a relevant clinical end point for HABP and/or VABP.

The only other clinical end point identified at the workshop that described an antibacterial treatment effect size was im-

provement of the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:F_IO_2), a marker of patient oxygenation status. In a prospective study by Luna et al [66], resolution of VABP over time was analyzed. The authors found that patients receiving initial effective antibacterial therapy had faster rates of improvement in PaO_2:F_IO_2 than did patients who received initial ineffective antibacterial therapy. This difference was found in both a Kaplan-Meier time-to-improvement comparison and by comparison of dichotomous outcomes at a defined time. Specifically, on day 3 after the diagnosis of VABP, the PaO_2:F_IO_2 decreased by 26% in patients treated with initial ineffective antibacterial therapy and increased by 3% in patients treated with effective antibacterial therapy (point estimate of the difference, 29%). Furthermore, improvement in the PaO_2:F_IO_2 has been shown to be an independent predictor of successful treatment of HABP and/or VABP [65], indicating the clinical relevance of the ratio as a marker for disease status. In its previous draft guidance for noninferiority trials of CABP, the FDA noted:

> The treatment effect for an end point such as clinical failure would likely be larger than that seen with a mortality end point. It is reasonable to assume that some of the patients in present-day trials would progress to death in the absence of rescue therapy. If the definition of clinical failure (including death) were applied to a historically conducted study or clinical trial, the clinical failure end point would be at least as great as the observed mortality. Thus, the treatment effect based on mortality in historical studies or clinical trials can be extrapolated to a composite end point in a present-day trial that includes both mortality and clinical failure [67, pp 24–25].

The societies concur with this logic, both for studies of CABP and for studies of HABP and/or VABP. The societies emphasize that limiting trials to a mortality end point is not consistent with standard clinical practice. Physicians routinely assess response to antibacterial therapy by evaluating clinical biomarkers, such as resolution of fever, normalization of WBC count, improvement in oxygenation, and successful extubation of patients receiving mechanical ventilation. Failure to consider the impact of antibacterials on such end points decreases the clinical relevance of the study and creates a risk that results of registrational studies will not extrapolate well to postapproval use of approved agents. Therefore, the societies strongly endorse additional research to allow use of clinical primary end points in future noninferiority trials. Specifically, analysis of the impact of discordant antibacterial therapy should allow documentation of the magnitude of treatment effect on these clinical biomarkers. Such investigations should be a priority research focus. When such results become available, they should be incorporated rapidly into acceptable clinical trial designs for noninferiority trials of HABP and/or VABP.

Hierarchical end point testing. Hierarchical end point testing was previously discussed during the CAP workshop [20, 68]. Hierarchical testing is particularly advantageous for trials of HABP and/or VABP, because it enables sequential assessment of both noninferiority and superiority primary end points in the same trial. Multiple primary end points are generally not appropriate for a clinical trial because of the concern of multiple comparisons testing. However, hierarchical testing obviates concern about multiple comparisons, because the end points are tested sequentially rather than concurrently. Specifically, end points are prospectively ranked such that the most important end point is tested first, and subsequent end points are tested only if significance is achieved with the preceding end point. Therefore, a trial could test for noninferiority in all-cause mortality for the primary efficacy end point, and if noninferiority is achieved, it can proceed to test for superiority in clinical end points (such as clinical response or resolution of signs and symptoms of disease, the standard primary end point used in HABP and/or VABP trials until recently [23, 24]).

If hierarchical primary end point testing is used in a clinical trial, hierarchical order should reflect loss of available information at each step in the hierarchy [68]. For example, in a trial assessing both all-cause mortality and clinical end points, mortality must be the first end point tested, because nonsurvivors are not available for assessment of clinical end points [69]. If the initial mortality end point does not meet statistical significance, the trial fails the primary end point, and subsequent end points in the hierarchy cannot be considered as primary end points. In the latter scenario, subsequent end points should either not undergo statistical testing or, if testing does occur, results should be considered as secondary, hypothesis-generating data rather than confirmatory end points.

The population for the primary end point analysis. The FDA recently released a draft guidance on the conduct of CABP clinical trials [21]. That guidance emphasizes the importance of establishing a microbial diagnosis in patients enrolled in noninferiority clinical trials of CABP. The need for a confirmed microbial diagnosis in patients enrolled in noninferiority clinical trials for HABP and/or VABP is even more important than that for CABP. Specifically, noninferiority trials carry a significant risk of a false-positive result (ie, failing to show a difference between 2 therapies, thereby establishing noninferiority) if substantial numbers of patients in either arm do not have the disease being studied. Nonbacterial causes of pulmonary infiltrates in hospitalized patients (eg, atelectasis, pulmonary contusions, noninfectious acute respiratory distress syndrome, viral pneumonia, pulmonary embolism, and alveolar hemorrhage) are common, are frequently indistinguishable from bacterial pneumonia, and will not respond to either the experimental or the comparator antibacterial agents used in a clinical trial. If substantial

numbers of such patients were to be enrolled in a clinical trial of antibacterial agents for HABP and/or VABP, an equal lack of efficacy in both arms could result in falsely apparent noninferiority. Therefore, culture-confirmed bacterial infection is critical for the integrity of a noninferiority study of HABP and/or VABP. Furthermore, enriching enrollment for patients infected with a bacterial pathogen will likely enrich for more ill patients, which is necessary to ensure constancy to the treatment effects seen in previous HABP and/or VABP studies [24].

For the aforementioned reasons, most workshop panel members agreed that the primary efficacy analysis should be conducted in a microbiologically confirmed population, in accordance with the recently released CABP guidance. More specifically, a mMITT population should be used, with efficacy analysis restricted to patients who receive at least 1 dose of study drug (the MITT population). Some panel members believed that coprimary analysis populations should be evaluated, including both the ITT and the mMITT populations.

An additional concern in HABP and/or VABP noninferiority trials is potential enrollment of a patient infected with an organism resistant to all protocol-specified regimens. Inclusion of patients infected with organisms resistant to all therapies in the primary efficacy analysis potentially decreases assay sensitivity of a noninferiority study. Inclusion of patients for whom neither therapeutic arm is likely to be effective makes noninferiority to the comparator regimen easier to achieve, even though neither therapy is more effective than placebo in this context. Therefore, patients infected by such an organism should be considered to be nonevaluable for the mMITT primary efficacy end point (but not for the safety ITT population).

One complexity is the lack of availability of established susceptibility breakpoints for the investigational agent, particularly if that agent has not been approved previously for another indication. In this case, whether a cultured microorganism is susceptible to protocol-specified therapy may be determined on the basis of the previously approved protocol-specified agents that have established susceptibility breakpoints (whether adjunctive therapy in the investigational arm or in the comparator arm), rather than on susceptibility to the investigational agent.

Feasibility of a microbiological primary end point. A microbiologic end point is a logical primary efficacy end point for HABP and/or VABP studies, but a variety of factors limit the possibility of such an end point [70]. Distinguishing persistent colonization from a persistent pathogen is often not possible when assessing postbaseline respiratory cultures [70]. Imputing microbiological eradication (ie, inability to obtain a proper specimen for follow-up culture because the patient is improved and no longer producing sputum) provides no additional useful information, compared with the information that is already available in a clinical response assessment. Serial quantitative cultures have the potential to ameliorate some of these limitations. However, obtaining follow-up invasive cultures is not standard of care and may expose the patient to risk of a procedure without altering the clinical course of the infection. Furthermore, thresholds for quantitative culture positivity are not well defined and may vary by microorganism. Therefore, evidence of microbiological eradication is not appropriate as a primary efficacy end point for a HABP and/or VABP study.

ENROLLMENT CRITERIA INCLUDING MICROBIOLOGICAL DIAGNOSTIC METHODOLOGIES

Enrollment clinical criteria. In selecting clinical enrollment criteria to be used in a HABP and/or VABP study, the goal is to increase the pretest probability of eventual culture-confirmed pneumonia. Combinations of appropriate clinical and radiographic criteria can be used to select patients more likely to be evaluable in the mMITT population. Clinical criteria relevant to the diagnosis of HABP and/or VABP are hospitalization for $\geq$48 h (or ventilation for $\geq$48 h for VABP); a new, progressive, or persistent pulmonary infiltrate on chest radiograph (read as consistent with or likely indicative of pneumonia by a radiologist); and at least 2 of the following signs: (1) temperature $<$36°C or $\geq$38.3°C, (2) WBC count $<$5000 cells/μL or $>$10,000 cells/μL; or (3) purulent sputum or endotracheal aspirate [41, 42]. These clinical and radiographic criteria are sensitive but not specific for establishing the diagnosis of HABP or VABP [42, 71, 72]. Nevertheless, these criteria are useful because the combination of clinical and radiographic criteria increase the pretest probability of disease [73, 74], thereby improving the positive predictive power of subsequent, confirmatory microbiology cultures for diagnosis of HABP or VABP. Therefore, the aforementioned clinical and radiographic criteria are appropriate inclusion criteria for HABP and/or VABP studies.

The Clinical Pulmonary Infection Score (CPIS) as a diagnostic tool for HABP and/or VABP was discussed extensively at the workshop. The CPIS is calculated from clinical and radiographic criteria very similar to the aforementioned enrollment criteria (ie, temperature, WBC count, radiographic findings, and tracheal secretions) but also includes estimates of hypoxemia (PaO_2:F_IO_2) and respiratory culture results [75]. Whereas the CPIS is somewhat more objective than the 3 individual clinical criteria, subjectivity remains inherent in the calculation of the CPIS, especially with regard to radiographic interpretation and quantification of tracheal secretions.

A CPIS $\geq$6 has been proposed to support the diagnosis of HABP or VABP [75]. However, data supporting the accuracy of the CPIS alone to establish a HABP or VABP diagnosis are mixed, and similar to the clinical criteria, the CPIS is most accurate for diagnosis when combined with

microbiologic confirmation of infection [41, 42, 76]. Twenty-two percent of patients with a CPIS <6 on day 1 can have their CPIS increase to ⩾6 by day 3, usually with the addition of microbiologic culture results [77]. Therefore, requiring the CPIS to be ⩾6 at enrollment may exclude up to one-quarter of patients who would be evaluable for the primary efficacy end point. Of note, the CPIS performs particularly poorly for patients with trauma and/or burns [78, 79], who comprise an increasingly important population of patients with HABP and/or VABP, because the incidence of these infections remains high in these contexts.

Because of the similarity of the information on which standard clinical and radiographic criteria and the CPIS are based, use of either clinical and radiographic criteria or the CPIS for enrollment criteria is reasonable. In either case, the purpose of these criteria is to increase the pretest probability of HABP and/or VABP; they must be used in combination with microbiologic confirmation to determine which patients are evaluable for the primary efficacy end point.

Severity-of-illness enrollment criteria. To ensure constancy with the historical studies used to justify the noninferiority margin for the primary efficacy end point, enrichment of the enrolled population for patients with relatively severe disease is necessary. The overall target all-cause mortality rate in the control arm should be 15%–20%. Therefore, calculation of a severity-of-illness scoring system is necessary as part of the study enrollment criteria to enrich for sufficiently ill patients.

Factors that define severe HAP and/or VAP have been characterized [41]. Such risk factors include admission to the ICU, respiratory failure (ie, the need for mechanical ventilation or need for >35% oxygen to maintain oxygen saturation >90%), multilobar pneumonia or cavitation, or evidence of severe sepsis or septic shock. Factors associated with an increased risk of mortality include prolonged mechanical ventilation before pneumonia, serious comorbidities, high Acute Physiology and Chronic Health Evaluation (APACHE) II score (ie, ⩾11 points), severe pneumonia, age >60 years, a high-risk pathogen, and delayed initiation of appropriate therapy [41]. Inclusion of these factors in enrollment criteria alone or as part of a disease severity scoring system (discussed below) would enable the study to achieve the target all-cause mortality of 15%–20% in the control arm.

Numerous disease severity scoring systems for HABP and/or VABP were discussed at the workshop, including the Simplified Acute Physiology Scoring, APACHE (II or III), the Therapeutic Intervention Scoring System, the Mortality Prediction Model, the Sequential Organ Failure Score, the Multiple Organ Dysfunction Score, and the Predisposition Insult Response Organ dysfunction system [80]. No clear consensus emerged from the workshop panel on the optimal choice for a severity-of-illness scoring system for a clinical trial of HABP and/or VABP. It was also noted that fewer pediatric disease severity scoring systems have been investigated or validated in neonates, infants, and children. The overwhelming consensus of the panel was that a disease severity scoring system should be used as an enrollment criterion for HABP and/or VABP studies. The choice of scoring system and the cutoff (both high and low) that should be used for the enrollment criterion should be determined by the study sponsor in consultation with the FDA and other regulatory agencies.

Other laboratory tests as enrollment criteria. Gram staining of a deep respiratory specimen may be useful at baseline for inclusion or exclusion of certain patients from enrollment, thereby enriching the mMITT population for the primary efficacy end point. For example, in a recent prospective study, Gram staining of bronchoscopically obtained specimens had a 90% sensitivity and 96% negative predictive value for VABP [81]. Similarly, in another study, results of Gram stain of either bronchoscopically or nonbronchoscopically obtained respiratory tract samples improved the diagnostic accuracy of the CPIS for VABP [82]. Incorporation of Gram stain results into the CPIS enabled early detection of 85% of patients subsequently confirmed to have VABP and enabled exclusion of 70% of those who did not have confirmed VABP. Therefore, a negative result of Gram stain of a sample obtained by bronchoscopy would be a useful tool to exclude patients from enrollment to enrich the mMITT population. In a systematic review, Klompas [74] reported that the positive likelihood ratio of Gram stain of a sample obtained by bronchosopy (but not by less invasive means) was high for VABP. Therefore, a positive result of Gram stain of a bronchoscopically obtained specimen could be useful in enriching patients for those likely to have VABP.

Gram stain results may also be important to include or exclude patients infected with organisms likely to be susceptible or resistant to the experimental therapy. For example, in a study of an investigational agent with a purely gram-negative spectrum, the observation of only gram-positive cocci on an adequately prepared and interpreted Gram stain of a deep respiratory specimen could be a useful exclusion criterion. Alternatively, in a study of an investigational agent with a purely gram-positive spectrum, the finding of gram-positive cocci on the Gram stain can be used to enrich the trial for patients who are likely to have HABP and/or VABP caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

Gram staining of deep lower respiratory tract specimens is also useful, because it provides information about leukocytes. The finding of <50% neutrophils by cell count analysis in a lavage specimen (either bronchoscopic or nonbronchoscopic) has a negative likelihood ratio of 0.05:0.1 for the diagnosis of VABP [74]. Therefore, the presence of <50% neutrophils in a lower respiratory tract specimen could be used as an exclusion criterion for enrollment (assuming that the information becomes

available shortly after the specimen is obtained), thereby enriching for patients who meet the mMITT criteria.

At many health care centers, Gram stain results are available within a short period and could be used as part of enrollment criteria to enrich the mMITT population. However, at many other health care centers (particularly, international centers), Gram stain results do not become available until the subsequent day, precluding their use as an enrollment criterion. Ultimately, the consensus of the workshop panel was that the decision regarding requirement for deep respiratory specimen Gram stain as an enrollment criterion should be made by the study sponsors, who can weigh the risks and benefits of its use for specific studies.

Finally, the potential for use of procalcitonin level as a diagnostic and/or enrollment criterion for HABP and/or VABP studies was discussed at the workshop [41, 70]. The relatively high negative predictive value of low procalcitonin level could make it useful for exclusion of bacterial infection. Therefore, use of a low baseline procalcitonin level to exclude patients who are unlikely to have a positive lower respiratory tract bacterial culture result may be reasonable, again enriching for patients more likely to be evaluable in the mMITT population.

Microbiological culture confirmation. There was general agreement that the primary efficacy end point should be analyzed in the mMITT population. Therefore, all evaluable patients must have a positive bacterial culture result. Nevertheless, microbiologic results are typically not available at the time of patient enrollment, and use of culture results as an enrollment criterion is, therefore, not practical. Instead, results of culture of specimens obtained at enrollment determine which patients to include in the mMITT population for the primary efficacy end point. Patients found to have a negative culture result should be considered to be nonevaluable for the primary efficacy end point (although they should be included in the ITT safety population). Experts at the workshop emphasized that dropping patients from the evaluable population after randomization is statistically acceptable in this context, because the microbiologic study on which the decision is based is not a postrandomization event (ie, the culture is performed at baseline, before initiation of any study treatment).

The definition of a positive culture result enabling inclusion of the patient in the mMITT population should be considered carefully in the study protocol to exclude cultures positive for nonpathogenic organisms. For example, specifying that a positive culture result requires moderate-to-heavy growth, by semi-quantitative or quantitative culture methods, of $\geqslant 1$ organism known to be causative of HABP and/or VABP (eg, gram-negative bacilli, *S. aureus, Hemophilus influenzae, Streptococcus pneumoniae,* and *Streptococcus milleri*) may be reasonable and was done in a recent multicentered, randomized trial of VABP [83].

One of the most contentious foci of discussion at the workshop was the proper technique for confirmation of the microbiologic etiology of VABP. Aside from debate about the degree to which bronchoscopically obtained culture specimens are superior in specificity to deep endotracheal aspirate specimens [74, 83–86], concern was expressed regarding the feasibility of obtaining quantitative, bronchoscopic specimens for culture from all patients in multinational clinical trials enrolling participants at dozens, if not hundreds, of sites worldwide [62, 63]. Ethical considerations also exist for routine invasive techniques for sample obtainment, such as bronchoscopy, in pursuit of a pathogen, especially for pediatric patients enrolled in HABP and/or VABP studies. This discussion reflected the lack of consensus of English-language national treatment guidelines on nosocomial pneumonia, regarding the need for bronchoscopic cultures, compared with noninvasive culture strategies, to diagnose nosocomial pneumonia in clinical practice [42]. The guidelines achieve consensus that a lower respiratory tract culture must be performed to support the diagnosis. However, the method by which such a culture specimen should be obtained differs among the various guidelines. Nevertheless, on the basis of published data indicating superior diagnostic accuracy, numerous panel members strongly preferred that quantitative cultures be used, regardless of whether the samples are obtained bronchoscopically, by a standardized method of mini-bronchoalveolar lavage [87], blind nonbronchoscopic obtainment of samples from distal airways [88, 89], or deep endotracheal aspiration [74]. Furthermore, some panel members believed strongly that bronchoscopically obtained quantitative culture specimens were preferred to those obtained by other methods.

In summary, the greater accuracy of quantitative culture of bronchoscopically obtained samples for the diagnosis of VABP must be weighed against the degree of invasiveness and feasibility because of the limited availability of quantitative cultures for HABP and/or VABP studies conducted at numerous sites internationally. Many panel members, but not all, concluded that carefully obtained deep endotracheal aspirate specimens may reflect a reasonable compromise between diagnostic accuracy and study feasibility.

The method for obtaining deep respiratory culture specimens in the context of VABP should be prospectively defined, and such specimens should be obtained by trained, experienced personnel. For example, a deep endotracheal aspirate requires that the suction catheter be advanced until resistance is met; only then should the specimen be taken. This method is not the usual technique for clearing secretions from proximal airways. Consideration may also be given to use of an external sterile suction catheter and suction trap rather than use of the in-line suction catheter, as was done in a multicenter, randomized comparison of quantitative bronchoscopically obtained cul-

ture samples and nonquantitative endotracheal aspirate samples [83].

If a patient with HABP undergoes bronchoscopy for clinical purposes, positive culture results for samples obtained through bronchoscopy would be appropriate for evaluation in the mMITT population of a clinical trial. However, most patients with HABP do not undergo bronchoscopy, and many workshop panel members believed that an invasive procedure that was not otherwise clinically indicated could not be mandated specifically for the purpose of obtaining specimens adequate for inclusion in the mMITT population of a clinical trial. These panel members believed that, for patients with HABP who cannot undergo bronchoscopy, positive culture results for semiquantitatively expectorated sputum samples are an alternative basis for inclusion in the mMITT primary efficacy population. Such sputum cultures should meet prespecified cytologic criteria (eg, $\geqslant$25 polymorphonuclear leukocytes $\pm$ <10 squamous epithelial cells per high-power field [90–92]). For pediatric patients with HABP, obtainment of appropriate expectorated samples is not realistic, further complicating the accurate identification of pediatric patients with HABP who are microbiologically evaluable.

There was considerable controversy over the proper methods used to obtain a deep respiratory culture samples for patients enrolled in HABP and/or VABP studies. For patients with either HABP or VABP, major emphasis should be placed on obtaining high-quality, deep respiratory samples for culture, irrespective of the method of obtainment. Prespecified protocols and criteria should be included in the clinical protocol to ensure the adequacy of the specimens, and the samples should be obtained by experienced, trained personnel.

Other means to obtain microbiologic confirmation of infection include positive pleural fluid culture results, positive blood culture results in the context of clinical and radiographic evidence of HABP and/or VABP, and urinary antigen testing. The societies underscore the need for advances in molecular diagnostic testing for establishing the microbiologic etiology of HABP and VABP. These advanced molecular diagnostic techniques could be used to establish the microbial etiology of HABP and VABP in clinical trials when such technologies become available and are validated.

ADVISABILITY AND DIFFICULTIES WITH STUDY OF HABP AND VABP IN THE SAME CLINICAL TRIAL RATHER THAN SEPARATELY

The acceptability of enrolling patients with either HABP or VABP in the same clinical trial was discussed at the workshop. Four predominant factors were central to consensus on this issue.

The first concern regarding enrollment of patients with HABP or VABP in the same clinical trial was the difference between patient drug exposure during HABP and that during VABP [63, 93]. An important subset of patients with VABP exhibit higher drug clearance and, therefore, lower antibacterial drug exposure, than do the majority of patients with HABP; both renal and hepatic clearance can be higher than expected, resulting in a bimodal distribution of exposure [63, 93].

The second factor affecting the appropriateness of combining patients with HABP and VABP in a single study is the microbiological etiology of the diseases. Although some differences in microbiology (eg, less *S. aureus* and MRSA, in particular, in patients with VABP) exist, in general, the microbial etiologies of the 2 types of infection have been similar in recent series [16, 41, 94–96]. Specifically, nonfermenting gram-negative bacilli, including MDR gram-negative bacilli, such as *Pseudomonas* and *Acinetobacter* species, cause a substantial proportion of both HABP and VABP. Key factors predicting whether MDR pathogens are the cause of infection include duration of hospitalization before the onset of infection (ie, <5 days imparts low risk and $\geqslant$5 days imparts higher risk), exposure to antibiotics during the preceding 90 days, or exposure to environments rich in MDR pathogens (eg, prior hospitalization, residence in nursing home, or receipt of dialysis or home infusion therapy). These factors predict MDR organisms equally for HABP and VABP. Therefore, a key factor determining the necessary antibacterial spectrum of both the experimental drug and the comparator regimen is not whether patients with both HABP and VABP are included, but whether there is presence or absence of individual patient risk factors for MDR organisms, such as the aforementioned factors and those mentioned in the ATS and IDSA guidelines on treatment of nosocomial pneumonia [40].

Third, the need to establish a microbiologic diagnosis for evaluable patients in the mMITT population may be problematic for a combined HABP and/or VABP study. Deep respiratory tract culture samples are readily obtainable from patients with VABP. However, an adequate deep expectorated sputum culture sample may be difficult to obtain from most patients with HABP. Excluded patients in a combined study are likely to be disproportionately patients with HABP. Practically, the time commitment and cost of an excluded patient may drive many investigators and sponsors to emphasize VABP enrollment.

Finally, the difference in mean severity of illness between patients with HABP and patients with VABP is an important consideration regarding whether studies should enroll both patient subsets. On average, patients with VABP are more severely ill and have higher predicted mortality rates, compared with patients with HABP [40]. Nevertheless, some patients with VABP (eg, young individuals without comorbidities who suffer trauma) may have a lower mortality rate than may certain subsets of patients with HABP (eg, those treated in an ICU). Furthermore, patients with HABP treated in the ICU

have severe disease with substantial risk of death, more akin to the typical mortality rate associated with VABP. Thus, enrollment of patients with HABP or VABP in a single study would require mechanisms to monitor the appropriate severity of illness and balance of severity of illness in the 2 randomization arms.

Considering the aforementioned factors, the potential for substantive differences between patients with HABP and patients with VABP exists. Therefore, enrollment of patients with HABP or VABP in the same study would only be feasible if these factors were accounted for in the study protocol. Specifically, 3 factors must guide the choice of enrollment of patients with HABP and/or VABP in a clinical trial. First, robust enabling data must be available to support the design of the study protocol for the definitive study. Specifically, data must be available to enable rational selection of a dose that provides adequate therapy, taking into consideration both drug exposure and susceptibility of likely organisms. For a study seeking to enroll patients with both HABP and VABP, the enabling data must provide a basis for a dosing rationale for both patient populations for the study drug. Second, patients must have microbiologic confirmation of disease for inclusion in the mMITT primary efficacy population. Finally, the severity of illness needs to be substantial for the total enrolled population, to provide constancy for the mortality rates in the historical studies used to justify the margin for a noninferiority study. Use of a severity-of-illness scoring system as an enrollment criterion (discussed further below) and potentially restricting or enriching enrollment for patients in the ICU could enable patients with HABP or VABP of similar disease severity to be enrolled in the same study.

In summary, noninferiority studies of nosocomial pneumonia could focus on HABP and/or VABP. In practice, patients with VABP will be easier to enroll in clinical trials, because positive, deep respiratory tract culture samples are easier to obtain from patients with VABP than they are from patients with HABP, and patients with VABP are more severely ill, on average, than are patients with HABP. However, advances in molecular diagnostics may make enrollment of patients with HABP more facile in the coming years. Combination HABP and VABP studies would be more complex to justify, because of the need for enabling data to support dose selection for patients with both HABP and VABP.

Finally, clear consensus existed at the workshop that patients with ventilator-associated tracheobronchitis, in the absence of radiographically confirmed pneumonia [41, 97], should not be enrolled in studies of antibacterial therapy for HABP and/or VABP. Clinical trials of tracheobronchitis for the purpose of establishing an indication for the treatment of this disease could be considered in the future, as understanding of the pathophysiology and clinical features of this disease become better understood.

APPROPRIATE STANDARD COMPARATOR AGENTS AND ADJUNCTIVE THERAPY

Selection of appropriate comparator therapy. The panel members at the workshop emphasized the need to use adequate and appropriate antibacterial therapy for all patients enrolled in studies of HABP and/or VABP [41, 42, 63, 98]. In general, individual antibacterial agents and specific combinations of agents, as well as dose and duration of therapy, that are recommended by the ATS and IDSA consensus guidelines on the treatment of HABP and/or VABP are appropriate for comparator drugs [40].

A major complicating factor is the variability of approved antibacterial drugs and especially their dosing regimens worldwide [62, 63]. Drug and dosing regimens should be standardized as much as possible in the protocol, despite variations in factors affecting pharmacokinetics (eg, weight and renal function). Ultimately, the selection of comparator regimens should take into consideration local microbiology surveillance data at participating study sites, such that local investigators are not forced by the study protocol to use inadequate antibacterial therapy for anticipated pathogens. To match appropriate therapy to likely MDR organisms, the protocol should specify different levels of intensity of comparator therapy and adjunctive therapy in the experimental arm on the basis of the presence or absence of the aforementioned risk factors for infection by an MDR organism [40–42].

Although comparator agents that have been previously approved for the specific indication under study have traditionally been used in noninferiority studies, the increasing prevalence of MDR and XDR pathogens makes the selection of an appropriate comparator for HABP and/or VABP studies increasingly difficult. For the treatment of infection with XDR pathogens that are resistant to all other options, it may be necessary to allow use of comparator treatments that do not have an approved indication for the treatment of HABP and/or VABP (eg, colistin and tigecycline). Furthermore, no comparator drug with activity against gram-negative bacilli has been approved for the treatment of HABP or VABP in pediatric populations; the only antibiotic approved for nosocomial pneumonia in children, linezolid, has no activity against gram-negative bacilli. Again, in trials of pediatric HABP and/or VABP, a protocol to specify unapproved comparator drugs may be necessary. In general, de-escalation of empirical combination therapy should be mandated by the protocol on the basis of microbiologic test results.

Adjunctive antibacterial therapy. One of the most complex decisions in a noninferiority trial design for HABP and/or VABP pertains to which adjunctive therapy should be allowed per protocol in the experimental arm [41, 42, 62]. A guiding principle is that the safety of patients enrolled in clinical trials cannot be compromised. Furthermore, study enrollment and clinical relevance are affected nega-

tively if protocol-determined regimens deviate from national treatment guidelines. Therefore, clinical trial design should be consistent with best practices. Because of the established increase in mortality when ineffective antibacterial therapy is initiated for the treatment of HABP and/or VABP, it is imperative that the initial empirical therapy in the experimental arm has activity against the infecting pathogens. Thus, failure to use combination comparator therapy for patients at risk of MDR pathogens is unacceptable. Adjunctive therapy also must be allowed per protocol for most experimental drugs for 2 primary reasons. First, the spectrum of most drugs does not include all the categories of pathogens relevant to HABP and/or VABP (ie, gram-positive cocci to include MRSA, gram-negative bacilli, MDR and XDR gram-negative bacilli, and anaerobes). Second, even if the experimental drug exhibits in vitro activity against each of the general categories of the likely organisms causing HABP and/or VABP, a very high probability of activity against individual microbial isolates (eg, $\geqslant$90% of likely isolates) must be shown, or a second agent should be added to increase the likelihood that initial therapy will be effective against likely isolates.

For experimental drugs with activity limited to gram-positive cocci, including MRSA, adjunctive therapy with an agent with activity limited to gram-negative bacilli is desirable. However, this approach is not always feasible or in the patient's best interests. For example, because many anti–gram-negative agents have some anti–gram-positive activity, aztreonam has been the preferred adjunctive agent in a number of studies. Unfortunately, resistance to this compound has reached substantial levels in *Pseudomonas aeruginosa,* and aztreonam is typically not effective against *Acinetobacter* species, an increasing cause of MDR HABP and/or VABP. Therefore, emphasis on aztreonam for gram-negative coverage in studies focusing on MRSA pneumonia is inappropriate and dangerous. Combination adjunctive therapy focused on MDR and/or XDR gram-negative bacilli should be used as indicated by the ATS and IDSA guidelines [40].

For experimental drugs with exclusive anti–gram-negative activity, adjunctive therapy for gram-positive cocci is required [40]. If the experimental drug is likely to treat virtually all (eg, >90%) strains circulating at the local site, including MDR and XDR strains, addition of a second gram-negative agent may not be necessary. If the experimental drug is not likely to treat virtually all strains of gram-negative bacilli, addition of a second gram-negative agent must be considered, based on ATS and IDSA criteria [40]. Empirical therapy with 2 drugs active against certain gram-negative bacilli is the standard of care for specific patient populations [40]. Thus, a newly approved antibacterial agent for HABP and/or VABP would be used empirically in conjunction with a second agent in patients at risk of MDR organisms, as was done during its registrational clinical trials. Therefore, addition at baseline of a second agent with activity against gram-negative bacilli does not necessarily affect the integrity of analysis of the efficacy of the experimental drug if use of combination gram-negative therapy was equally applied to the experimental and comparator arms of the randomized study and if adjunctive therapy was terminated promptly after microbiologic confirmation of susceptibility becomes available. Of note, addition of a second agent with activity against gram-negative bacilli is yet another reason why double-blinding of the study should be conducted, because open-label use of the experimental drug could lead to bias in selection of patients requiring a second gram-negative agent. Preplanned analysis of the frequency of addition of a second agent with gram-negative activity would provide reassurance that the protocol-specified criteria for a second agent were applied evenly to both arms. In all cases, adjunctive therapy should be eliminated or narrowed as much as possible immediately after availability of microbiologic confirmation of the etiological agent(s).

The most complicated scenarios arise for experimental drugs that have activity against both gram-negative bacilli and gram-positive cocci not including MRSA (eg, imipenem-cilastatin) and for agents with a limited spectrum of activity against one or a few specific types of gram-negative bacilli that are common causes of HABP and/or VABP (eg, a drug or biological with exclusive activity for MDR and/or XDR *Pseudomonas* or *Acinetobacter* species, but not other organisms). The former situation is complicated because the adjunctive antibacterial therapy targeting MRSA is likely to have overlapping activity with the experimental drug against non-MRSA gram-positive organisms (eg, methicillin-susceptible *S. aureus* or streptococci). Patients determined to be infected with MRSA would be excluded from the mMITT population because of the absence of activity of the experimental drug against MRSA. However, patients determined to be infected with methicillin-susceptible *S. aureus* or streptococci would be included in the mMITT population. For double gram-negative bacilli coverage, addition of an adjunctive agent with activity against MRSA does not necessarily affect the integrity of analysis of the efficacy of the experimental drug against other gram-positive organisms if such adjunctive MRSA therapy was applied equally to the experimental and comparator arms and if adjunctive therapy was promptly terminated after microbiologic confirmation of susceptibility became available.

For agents with a limited spectrum of activity against one or a few specific types of gram-negative bacilli, the mMITT population should be limited to the organisms for which the therapy has activity to avoid confounding effects of additional adjunctive therapy. Such an agent might be more appropriately studied in a superiority study of adjunctive, combination therapy versus monotherapy for the targeted organism.

In all cases, adjunctive therapy should be eliminated or narrowed as much as possible immediately after availability of microbiologic confirmation of the etiologic agent(s). A prespecified analysis of the duration of adjunctive therapy in both study arms would provide reassurance about the comparability of narrowing of therapy in both study arms.

Cessation of study therapy based on susceptibility testing. Final susceptibility interpretive criteria are not established for an investigational agent until after phase 3 data become available. Furthermore, susceptibility testing for an investigational agent may need to be conducted at a central laboratory, because clinical laboratories may not have the capacity to test susceptibilities for nonapproved drugs. Therefore, results of susceptibility testing for an investigational agent may not be available in real time during treatment of the patient and, even when available, may not be interpretable with respect to definitive breakpoints until after the end of the phase 3 study.

Even for commercially available adjunctive or comparator therapies, susceptibility testing results may not return for 48–72 h. Because of this delay, in blinded studies, an acceptable approach has been for the investigator to determine treatment discontinuation primarily on the basis of the patient's response to therapy and not on the basis of susceptibility data. For example, in situations in which the isolated pathogen appears to be resistant to both of the treatment regimens, a salutary clinical and radiographic response would ethically allow continuation of blinded study therapy. By contrast, a patient infected by such an organism who experiences clinical failure should have study treatment discontinued (but they should not be withdrawn from the study), regardless of the susceptibility pattern.

Prior antibiotic therapy. In contrast to CABP, for which a published study suggested a treatment effect of even a single dose of antibacterial therapy before enrollment in a clinical trial [99], no such data are available on the impact of prior therapy for HABP and/or VABP. The microbiology of HABP and/or VABP is clearly distinct from that of CABP, with HABP and/or VABP typically caused by MRSA or gram-negative bacilli that are more refractory to eradication than are CABP pathogens. *S. pneumoniae* and *H. influenzae* infrequently (<5%) cause HABP, and when they do, it is usually in the context of early-onset (<5 days) disease [40]. Underlying disease and comorbidities are, on average, more numerous and severe for the hospitalized population with HABP and/or VABP, tending to make microbial eradication more difficult than for CABP. Finally, VABP occurs in the setting of a foreign body (the artificial airway), making bacterial eradication far less likely after a single day of therapy. Therefore, the consensus of the workshop panel members was that a single day (not dose) of prior appropriate antibiotic therapy is unlikely to significantly affect cure rates for HABP and/or VABP. Patient enrollment before initiation of nonstudy antibiotic therapy, if possible, is recommended, but ≤24 h of prior therapeutic drug exposure should be allowed per protocol for studies of HABP and/or VABP.

FACTORS BY WHICH ENROLLMENT SHOULD BE STRATIFIED

Randomization should enable balance in important baseline characteristics between study arms. Nevertheless, stratification for factors known to affect the likelihood of treatment success provides an additional layer of security that the 2 study arms will be balanced for these key factors. Stratification during enrollment is recommended for risk factors for infection due to a MDR and/or XDR organism, as elaborated elsewhere and in the ATS and IDSA guidelines [40], and for factors increasing disease severity and/or mortality risk, as discussed above [41].

If patients with both HABP and VABP are enrolled in the same study, the primary stratification should be by disease type (HABP vs VABP). Most panel members also believed that patients should be stratified by a disease severity scoring system to ensure adequate balance between the arms of the study. The scoring system and cutoff values to be used for stratification should be chosen by the sponsor.

TRIAL INTEGRITY ISSUES, INCLUDING BLINDING, INTERNATIONAL SITES, AND THE NEED FOR A CLINICAL TRIALS NETWORK

Should studies of HABP and/or VABP be blinded? There was consensus among the workshop participants that studies of HABP and/or VABP should be double-blinded (patient and observer). Minimization of all forms of bias is crucial in a noninferiority trial, and blinding of the observer is necessary to minimize bias. Blinding of the clinical care team and any end point adjudicators is also desirable, if possible.

Nevertheless, complexities of study blinding are likely to be encountered in HABP and/or VABP studies. Some possible comparator or adjunctive antibacterial agents require monitoring of serum concentrations (eg, vancomycin and aminoglycosides), and many antibacterial agents require dose adjustment for renal dysfunction, which is common in patients enrolled in HABP and/or VABP studies. Adjustments of dose in these contexts require unblinded study personnel to evaluate results of drug concentrations and renal function. Such unblinded personnel should not participate in any other aspect of study conduct or end point assessment, aside from appropriate alteration of drug doses. Furthermore, drug concentrations should not be placed in the patient's medical record to avoid unblinding the patient's assigned study arm.

Other complications to study blinding are the use of multiple antibacterial agents with varied administration schedules in the control arm and as adjunctive therapy and the potential for antibacterial agents used as comparators to differ from those

used as adjunctive therapy in the experimental arm. Double-dummy designs should be used, if possible, for dosing regimens that differ between the control and experimental arms, although the additional fluid volume required may limit feasibility. Colored infusion solutions also complicate blinding and may require colored tubing or opaque tubing sleeves to maintain blinding.

Pediatric clinical trial issues. The societies support inclusion of pediatric patients in HABP and/or VABP research protocols, if possible, because of the need to define appropriate therapy for these patients. Complexities of pediatric studies of HABP and/or VABP are discussed further in this supplement [98], with an acknowledgment that invasive diagnostic techniques may not be widely used at study enrollment for neonates, infants, and children, requiring some degree of extrapolation of drug exposure and/or efficacy data from adult populations. Collection of adequate safety data for each pediatric age group, from extremely low birth weight premature infants to adolescents, remains an important goal for pediatric investigations. Inclusion of children earlier in the overall drug evaluation programs than currently exists for HABP and/or VABP registration trials is also important, because MDR pathogens exist in hospitalized pediatric populations. Postponing the start of a pediatric program until the conclusion of large phase 3 adult studies results in an unacceptable delay in providing essential information to clinicians on medically needed drugs for children [98].

National and international sites of enrollment. Recent clinical trials of HABP and/or VABP have enrolled at sites in multiple countries on multiple continents [62, 63]. The complexities of conducting such studies and the resources required to enroll patients at such sites are considerable. Indeed, it was estimated at the workshop that recent studies of HABP and/or VABP cost $60,000–$80,000 per patient enrolled, resulting in phase 3 trial program costs of >$75 million per study [62, 63]. The consensus of the panel was that it was simply not feasible to conduct a HABP and/or VABP study strictly in the United States because of limited numbers of eligible patients and especially because of (1) highly restrictive and complex protocol entry requirements [62, 63], which limit potential patient and investigative site participation; (2) recent changes in reimbursement for patients with nosocomial infections, which could lead to underreporting of HABP and/or VABP cases [100]; and (3) the likely reluctance of severely ill patients and families to participate. Because of these factors, enrollment would be impossible to complete solely in the United States within a reasonable period. Therefore, it is necessary that studies of HABP and/or VABP be allowed to enroll patients internationally.

International enrollment adds complexity to study protocols for a variety of reasons [62, 63], including (1) variations in local microbiology that require prespecification of a sufficiently broad comparator antibacterial regimen to be effective at all sites [16]; (2) variations in standard of care and, thus, availability of microbiologic techniques and other laboratory data; and (3) variations in quality of data that can be gathered and abstracted from study sites. Such factors must be considered by the study sponsor when selecting study sites. Several of the workshop participants emphasized that the reported frequency of HABP and/or VABP is decreasing in medical ICUs and that emphasis should be placed on recruiting patients from trauma and/or surgical and burn ICUs to improve enrollment rates [80, 97].

A clinical trials network for studies of HABP and/or VABP and other infections. Noninferiority trials are particularly susceptible to issues of study integrity [25, 26]. Collection of inadequate data, enrollment of incorrect patients, improper randomization, and myriad other potential issues in study conduct all increase the risk of incorrectly rejecting the null hypothesis and establishing noninferiority of an experimental drug that is actually less effective than the comparator regimen. Specifically for HABP and/or VABP, experienced study sites are highly desirable, as are sites with a high level of medical technology and training where preferred microbiologic techniques (eg, bronchoscopic and/or quantitative cultures) can be used, similar adjunctive management of critically ill patients can be reliably performed, and other crucial elements of study conduct can be assured. An established network of clinical trial sites would improve the quality of study data, enable timely enrollment of patients, and result in a significantly higher proportion of patients being enrolled in the United States, helping to ensure that the data from the study are relevant to the US population. The need for such a clinical trial network, based on similar concerns, has been discussed elsewhere [101]. The societies reiterate the need for such a network to help support conduct of clinical trials for HABP and/or VABP, as for other diseases.

CORE COMPONENTS OF A HABP AND/OR VABP CLINICAL TRIAL PROGRAM

Although the major focus of the workshop was on the design of individual HABP and/or VABP clinical trials, the panel discussed the core components of a clinical trial program, because successful development of new drugs for patients with HABP or VAP requires that both the scientific and regulatory requirements and the regulatory indication are clearly defined for each trial [63].

An essential feature of such a program is a robust set of enabling data before initiation of phase 3 trials [63, 93]. Relevant enabling data include prior therapeutic experience with the class, preclinical data (eg, in vitro drug-susceptibility testing and activity in animal pneumonia models), and clinical data (eg, pharmacokinetic-pharmacodynamic modeling for target attainment in plasma and, when possible, in the lung, and possibly phase 2 data on HAP and/or VAP, especially for novel an-

tibacterial classes). Although the state of the art allows prediction of efficacious dosing regimen(s), important physiological factors altering drug exposure and unexpected distributions of infecting pathogens or drug-susceptibility profiles can be problematic.

Because of the scientific and logistical issues associated with the study of HABP and/or VABP (as discussed at the workshop), data from one respiratory indication could be used to inform regulatory decisions about another. For example, because a CABP draft guidance has been issued by the FDA, one paradigm for registration could be the successful conduct of a noninferiority trial on both moderate-to-severe CABP and HABP or VABP to support an indication for pneumonia, including both community and nosocomial cases. As was discussed at the workshop, there is precedence at the FDA for granting a second indication to a drug on the basis of one successful clinical trial if that drug had previously been granted a related indication on the basis of the results of 2 successful clinical trials. Therefore, successful completion of 2 clinical trials of CABP and 1 clinical trial of HABP and/or VABP could lead to a general pneumonia indication. Furthermore, the enabling data (ie, preclinical in vitro and animal model data, clinical pharmacokinetic-pharmacodynamic data, and early-phase clinical data) are generally predictive of antibacterial efficacy in phase 3 clinical trials. Therefore, if a development program had strong enabling data, granting of an FDA indication for the treatment of pneumonia after successful completion of a trial for CABP and a trial for HABP and/or VABP would be reasonable.

FINAL COMMENTS

The societies that cosponsored the HABP and/or VABP workshop advocate for patients and their health care providers. The positions presented here are not motivated by advocacy for industry. The convergence of lack of antibiotic development and increasing rates of antibiotic resistance in lethal bacterial pathogens [17], particularly organisms that cause HABP and VABP, has created a dangerous public health problem. As physicians and public health advocates, the workshop panel emphasizes that patients need new drugs for HABP and/or VABP. Furthermore, because a mean period of $\geqslant$10 years is required to complete development of a new drug, strengthening of the antimicrobial pipeline now is essential to meet anticipated needs in $\geqslant$1 decade. An important step to enhance the discovery and development of new antibiotics is clarification of FDA guidance for future clinical trials of antibacterial agents for HABP and/or VABP.

The current uncertainty in acceptable designs for clinical trials of HABP and/or VABP contributes to disincentives in the discovery and development of new drugs for these diseases. After a related workshop on CABP, the FDA released a guidance document that provided clear directions for conduct of trials of CABP. The societies desire similar approval and dissemination of clear and defensible guidelines for future clinical trials of new antibacterial agents for the treatment of HABP and/or VABP.

MEMBERS OF THE WORKSHOP ON ISSUES IN THE DESIGN AND CONDUCT OF CLINICAL TRIALS OF ANTIBACTERIAL DRUGS FOR THE TREATMENT OF HOSPITAL-ACQUIRED BACTERIAL PNEUMONIA AND VENTILATOR-ASSOCIATED BACTERIAL PNEUMONIA

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PhRMA

February 25, 2011

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061
HFA-305
Rockville, MD 20852

Re: Docket No. FDA-2010-D-0589: Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment.

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) welcomes the opportunity to provide comments on the above referenced draft guidance Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia issued by the Food and Drug Administration (FDA).

PhRMA represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members alone invested an estimated $45.8 billion in 2009 discovering and developing new medicines. Industry-wide research and investment reached a record $65.3 billion in 2009.

PhRMA appreciates the efforts of FDA in providing updated guidance regarding the clinical development of antimicrobial drugs for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). In sponsoring and conducting clinical research, we consider such guidance helpful by making the requirements for drug development programs more transparent for the industry.

However, we do have a number of concerns regarding the draft guidance, which PhRMA believes would make clinical trials for the HABP/VABP indication extremely difficult to conduct. Given the responsibility of the FDA to serve and protect the public health, which is shared by the members of PhRMA, we believe that implementation of the draft guidance as written would harm patients by making it more difficult for the development of new and novel compounds being made available for clinical use in the foreseeable future.

Our primary areas of concern focus on the primary efficacy endpoint, prior use of antibacterial drugs, the relevance of patient-reported outcome (PRO) measures, the approach taken to set a non-

inferiority margin, and general conduct of the HABP/VABP clinical trials as follows:

1) All-cause mortality (as the primary efficacy endpoint) at 28 days after randomization is not an outcome that is used or appreciated in clinical practice, would not be useful to guide therapy, and is highly confounded by patient risk factors having little, if anything, to do with the infectious process under treatment

2) The requirement of microbiologic confirmation is inconsistent with treatment guidelines which emphasize the clinical syndrome in treatment decisions

3) Substantial restrictions on prior use of antibacterial drugs will make enrollment infeasible

4) The suggestion that a PRO measurement be used for symptom assessment fails to consider the severity of illness of patients with nosocomial pneumonia

5) The approach taken to determine M1 and M2 is excessively conservative

International harmonization remains an additional area of concern. Specifically, differences in guidelines from other regulatory health authorities must be resolved to facilitate global development and registration of critically needed antimicrobial agents. Agreement on internationally acceptable comparator antibiotics is another aspect of harmonization that must be considered.

Finally, we offer additional comments regarding specific line items of the draft guidance.

Herewith we provide a general statement regarding the draft guidance and a detailed discussion of our prioritized primary areas of concern, followed by comments to specific points in the draft guidance.

General Statement

Trials in nosocomial pneumonia (NP) or for the HABP/VABP indication are very difficult to conduct as evidenced by several recent submissions (linezolid, doripenem, telavancin, ceftobiprole). Enrollment rates have been consistently low (e.g., approx. 0.1 patient/site/month in the telavancin trials) under already existing guidelines, and these rates are expected to decline further as measures to reduce the incidence of nosocomial pneumonia are implemented more widely.

The proposed new Draft Guidance will further restrict patient enrollment, resulting in more complex and lengthy trials. We note that several new requirements for eligibility and treatment run contrary to clinical practice, do not follow current ATS/IDSA Guidelines for NP diagnosis or treatment, and select for an unrepresentatively small subset of patients with HABP/VABP.

While PhRMA members, of course, support efforts to incorporate new science into protocols for HABP/VABP, the combination of several new and challenging provisions in the draft guidance requirements (see Main Areas of Concern detailed below) stand to create serious feasibility issues for sponsors, which ultimately could harm patients. We believe that striving for the study that eliminates all confounding factors will not be implementable and will not serve either the patient population or the medical community. Multi-drug resistant (MDR) organisms are on the rise at a time when the late stage pipeline of new antibiotics is essentially empty. We are concerned that this threat to the public health will not be met as antibiotic development stalls because of increasing regulatory hurdles. HABP/VABP is an indication where antibiotics have historically made a huge difference in outcome, and PhRMA members believe that feasibility issues should not be ignored in the quest to innovate. We advocate judicious use of new information for inclusion into trial protocols as outlined below.

Detailed Discussion of Primary Areas of Concern

1. *All-cause mortality (ACM) as the primary efficacy endpoint at 28 days after randomization*

ICH E9 states that the primary analysis should be the one that is most relevant, the analysis of greatest interest. To patients and clinicians, survival is clearly important but so is response to initial course of therapy, lack of adverse events and lack of complications. The 'quality' of survival, i.e., the patient's life status is important to capture in addition to mere mortality information. We believe that bacterial eradication is the first step that influences other biologic response parameters and clinical criteria (like normalization in WBC count and body temperature, improved oxygenation, etc) remain useful and sensitive markers of response to antibiotic therapy.

Death, while definite, is a nonspecific outcome and, in HABP/VABP (more than in other indications like ABSSSI, CABP, or cIAI), is a reflection of the severity of the underlying disease. Data suggest that the majority of deaths that occur during or after an episode of NP may be due more due to the underlying medical conditions rather than directly caused by the NP [American Thoracic Society / Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am. J. Respir. Crit. Care Med. 2005; 171:388]; [Flanders S. Nosocomial Pneumonia: State of the science. Am J Infect Control 2006).; 34: 84). It stands to reason that a late assessment of mortality will capture more deaths unrelated to NP or the efficacy of the antibiotic intervention. Given that treatment for VAP is now reduced to about 8 days and only rarely does treatment last as long as 14 days, we believe that the efficacy of antibiotic therapy should possibly be assessed at an earlier time point (than recommended in the draft guidance), i.e., shortly after the end of therapy, to avoid confounding the antibiotic effect by the impact on mortality of unrelated events and conditions affecting mortality. We do, however, understand that the mortality rates at an earlier time point may not achieve that projected in the guidance for which a 10% NIM non-inferiority (NI) margin would be justified. This requires further discussion and consideration. For all these reasons, ACM was uniformly rejected as an

endpoint by several professional societies (IDSA, ATS, ACCP, and SCCM). [Clin Infect Dis Suppl.1, Aug. 2010: Workshop on Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia].

As pointed out by intensivists at the HAP/VAP workshop [Workshop co-sponsored by the Food and Drug Administration (FDA), the Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS), the Society of Critical Care Medicine (SCCM), and the American College of Chest Physicians (ACCP): Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP). March 31 & April 1, 2009, Silver Spring, MD], physicians can nowadays keep a patient artificially 'alive' on a ventilator. Presumably, such cases would be considered 'survivors' by the criteria of the current draft guidance. The opposite problem can occur in patients with a "Do Not Resuscitate", "Do Not Intubate" or "Comfort Care Only" orders: these patients, by not seeking aggressive supporting medical care, would be allowed to die early and be counted as non-successes in the primary ITT-driven efficacy evaluation thereby artificially inflating mortality for the assigned treatment. Either scenario leads to outcome assignments which have little to do with the particular treatment regimen.

Recommendations:

We believe that it is important to capture several outcome dimensions at different time points when studying HABP/VABP patients. ACM at Day 28 is an important endpoint but has the problem of non-specificity for the pulmonary disease process and non-sensitivity to drug effect when measured so late after a course of antibiotic therapy. Thus, day 28 ACM lacks the characteristics to be a useful primary endpoint.

We are not aware of data suggesting that 28-day mortality has greater sensitivity to treatment effect than currently used criteria of clinical response and functional performance. We also are not aware of any examples where the current clinical endpoint (determined at TOC) produced discordant results with mortality rates. In addition, there are data (albeit limited) to support the use of clinical endpoints: both duration of fever and ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FIO_2) have been shown to be significantly impacted by effective vs ineffective ("placebo") antibacterial therapy [Spellberg B. Clin Infect Dis 2010; 51(S1):S150–S170].

Mortality as an outcome has never been neglected in HAP/VAP clinical trials and is an integral part of the clinical response evaluation at TOC. It is also captured as a secondary response measure at Day 28 in the safety analysis.

Therefore, PhRMA members recommend keeping clinical efficacy at TOC as the primary efficacy endpoint. We agree that mortality at Day 28 could be a valuable secondary endpoint. We also agree that the concept of 'attributable mortality' is too subjective in nature, lacks standardization and should not be used. The new guidance should provide a path for such trials based on clinical outcome.

2. *Requirement for positivity at entry (mITT)*

Lack of a cultured pathogen does not mean that the pneumonic process is not bacterial in origin. A recent article and a comprehensive review of the contribution to diagnosis by invasive measures conclude that neither qualitative nor quantitative sampling microbial analysis of respiratory secretions improve the diagnosis of ventilator-associated pneumonia compared to diagnosis based solely on clinical criteria [Miller J.. National nosocomial infection surveillance system: from benchmark to bedside in trauma patients. J Trauma 2006;60:98-103]; [Rea-Neto A et al. Diagnosis of ventilator-associated pneumonia: a systemic review of the literature. Crit Care 2008;12:R56. Epub 2008 Apr 21]. Despite the advent of quantitative cultures and techniques to avoid contamination, difficulties distinguishing colonizers from true pathogens remain.

In clinical practice, empirical therapy must be started quickly before pathogens are identified. Invasive diagnostic procedures, like bronchial alveolar lavage (BAL) or protected specimen brush (PSB) are not even routinely conducted at academic centers. Given the lack of data showing that invasive methods to obtain samples for pathogen identification improves outcomes, current recommendations by ATS should be heeded.

Recommendations:

We agree with the need to make every effort to document a bacterial etiology. PhRMA members believe that demonstration of a positive respiratory culture is useful in determining per pathogen outcomes but is not essential to determine an overall treatment effect (as explained above). The clinical diagnosis of HABP/VABP does not hinge on recovery of a pathogen. For reasons of practicality and generalizability of results, patients with signs and symptoms of NP should be eligible for enrollment as long as they meet rigorous clinical and radiologic criteria. We agree that work-up should include respiratory cultures (sputum and endotracheal samples) to substantiate the specific bacterial etiology. In the NP trials used by FDA for determination of the non-inferiority margins, a valid entry pathogen was not required. Nonetheless, the benefit of antibiotics was clearly evident.

We recommend that the ITT population remain the primary efficacy population. Limiting the primary analysis population to the mITT subset excludes too many patients with true bacterial pneumonia. Nonetheless, we expect that a sizeable subset would meet mITT criteria and allow for a protocol-driven pre-specified secondary analysis. It is hoped the advent of rapid diagnostic tests will make it easier to exclude non-bacterial etiologies in the future.

3. *Exclusion of prior use of antibacterial drugs*

As in previous guidelines, the new draft guidance allows for only one exception to the prior-antibiotic exclusion: patients with failure of prior antibiotic therapy **and** positive respiratory cultures. This is a reasonable provision to maintain. However, the newly proposed restriction

of enrollment to patients without any prior antibiotic exposure for a full month unnecessarily excludes too many patients. Patients who received antibiotics for trauma or surgery, for peri-operative prophylaxis or central line infection, or for conditions unrelated to the pneumonic process should be considered candidates for enrollment and not be summarily excluded. Indeed, a recent study from Brazil found that prior antibiotic therapy was a risk factor for the development of VABP [Rodrigues P. Ventilator-associated pneumonia: epidemiology and impact on the clinical evolution of ICU patients. J Bras Pneumol. 2009;35:1084-91]. There is no reason to believe that in such cases exposure to non-study antibiotics would confound the efficacy analysis.

In two studies of community-acquired pneumonia comparing daptomycin with ceftriaxone, the influence on outcomes of a single dose of a short-acting non-study antibiotic prior to starting protocol-driven therapy was negligible [Pertel P., Clin Infect Dis. 2008; 46:1142]. In this retrospective analysis, prior antibiotics seem to have affected the treatment outcome only when given for a full 24 hours. We would argue that this result may be due to the fact that *S. pneumoniae*, the predominant organism in CAP, is exquisitely sensitive to antibiotics and prone to autolysis. Because HABP/VABP is often caused by hardier organisms (*Enterobacteriaceae*, MRSA/MSSA, non-lactose fermenters), and, in the case of VABP, the presence of an endotracheal tube retards bacterial eradication, even 24-hrs of prior antibiotic use is unlikely to significantly affect outcomes. This was shown in the series of studies compiled by FDA in which 24-h of non-study antibiotics was permitted without obliterating a significant 40% mortality benefit. In addition, recent clinical trials in HABP/VABP (e.g. telavancin and others) would have data to address this concern, and we respectfully request that FDA analyze these data before final consideration of this recommendation.

Timing of antibiotic administration has a direct effect on treatment outcome in NP, making it imperative to administer antibiotics as soon as the diagnosis of NP is made. Furthermore, because the NP population is frequently debilitated or sedated, consent is often required from guardians, delaying enrollment into drug trials. We are concerned that eligible patients will inevitably receive non-study antibiotics while study procedures required for entry are completed.

In the ATTAIN telavancin program, only 15% of patients met the most rigorous condition of no prior antibiotic use, and this does not take into account the additional proportion of patients who were already excluded because they received >24 hours of prior antibiotic therapy. Combined with the additional requirement for documentation of a valid organism at entry, PhRMA members believe that the required number of mITT cases cannot be collected in a reasonable time frame.

Recommendations:

PhRMA agrees conceptually that confounding effects from other antibiotics should be minimized as much as possible. We share the concern that prior antibiotic therapy, especially if prolonged, will influence the recovery of organisms from respiratory samples. While the exclusion of patients who received any prior antibiotic therapy would be ideal, in a real world situation such patients are exceedingly difficult to identify and are not representative of the larger NP population. This was borne out in the large telavancin program where only 15% of patients had no prior antibiotic exposure.

Therefore, we ask that the Agency reconsider this restriction and permit the use of short-active antibiotics prior to starting study drugs.

Logistical reasons and good medical practice dictate that patients receive antibiotic therapy without delay once the diagnosis of NP is established. Therefore, we believe that antibiotics cannot be delayed for study-related reasons once the diagnosis of HABP/VABP is made. For reasons of trial integrity, the administration of short-acting non-study antibiotics should be allowed (for $\leq$ 24 hrs) with the intention to keep this exposure to a minimum.

4. *The use of a patient-reported outcome (PRO) measurement for symptom assessment*
The Guidance states that a PRO tool should be used to defend clinical endpoints based on symptom assessment. No such PRO tool currently exists. If a PRO tool were to be developed, it would have to go through a series of pilot studies with iterative selection of response parameters to identify the best set of predictors. These results would have to be validated and further refined. We doubt that such an effort will be ultimately successful in the very sick patient population with HABP/VABP who are obtunded, sedated and possibly on a ventilator. That such a tool, once validated, would enhance our current methods to assess treatment effect, is highly theoretical. Clearly, developing a PRO tool for HABP/VABP creates a separate lengthy work stream with low likelihood for success or benefit.

Furthermore, the added value to be derived from the tremendous effort required to develop such a PRO tool is called into question as the Agency only considers it a secondary endpoint (ACM being the primary efficacy endpoint).

Recommendations:

Currently, a validated PRO tool for this indication does not exist and may be unattainable. Recommending the development of a validated PRO tool for symptom assessment within a trial (or even a product development program) is therefore unrealistic. Experience with development of PRO tools for other indications (like AECB) has shown that this is a multi-year process. We believe that antibiotic testing in HABP/VABP should not be held hostage by the lack of a validated PRO measure in this indication.

We believe that guidance should be based on existing science, not on conjecture about the value of alternative approaches which have not yet been established as useful. PhRMA members believe that clinical parameters using objective criteria and sequential observations and data (labs, chest imaging studies, pulmonary function testing [PFT]) are well suited to assess clinical response; after all, it is this clinical approach which guides patient therapy. PhRMA members remain interested in PRO tools once available and validated, but feel that sponsors should not be expected to develop complex PRO instruments as part of an antibiotic test program.

5. *The estimation of M1 and derivation of M2*
Reference is made to FDA's approach to assess treatment effect of antibiotics (Appendix A, Lines 765-994) which resulted in a historical 29% treatment effect with a ~30% discounting, resulting in an M1 of 20% and M2 of 10%.

PhRMA concerns about the method to derive M1 and M2 were already raised in our previous responses [to ABSSSI and Non-inferiority draft guidances, in letters dated Nov. 23, 2010 and June 1, 2010, respectively]. We believe that

- there is double-discounting of the historical treatment effect by applying 2 arbitrary, non-scientific adjustments to achieve a 'conservative, reliable' M1, which is then further discounted to achieve the M2 (or NI) margin
- there is bias in the selection of reference studies, and
- the sole reliance on the frequentist approach is flawed as it ignores the large body of supportive data from animal testing, PK/PD, and lung penetration studies which result in a low M1 and M2, with the effect of enlarging study size considerably.

By 'double-discounting' we refer to the method of using the delta between "lower-and-upper CI boundaries" approach, and applying to this already conservative estimate a further 30% discount to determine M1.

While the draft guidance mentions the rationale for discounting, it is unclear how these factors were quantitatively established. As it stands, double-discounting results in NI margins less than half of the originally observed treatment effect (using the FDA 8-study data set). Such arbitrary discounting misrepresents the antibiotic effect size and discredits the approach to establish evidence-based NI margins. We do not believe that this mix of statistical science and arbitrariness provides a better reference frame than the existing practice where NI margins are based on clinical judgment. M2 should be justified on the basis that it must be less than 20% (M1) but be clinically reasonable, and not by arbitrarily discounting M1.

We would like to get further clarification how the odds ratio method will be applied if observed mortality in a trial falls below 20%. The draft mentions that this topic should be discussed when a protocol is being developed. PhRMA would appreciate if the Agency could

expand the applicable section in the Guidance document to include, among others, guidance on defining NI margins around the odds ratio.

The characteristics of the historical putative placebo controls – those patients who received inadequate or delayed therapy – may or may not be representative of the overall HABP/VABP population enrolled in a particular study. This makes the generalizability of closely matched subject groups limited. In particular, the underlying illnesses among the historical non-randomized studies are not described. It is these underlying conditions that may be most important to identify the reason for increased mortality.

Recommendations:

The FDA conducted a thorough literature review to estimate drug effect based on results from well-conducted trials in the indication. Not surprisingly, the Agency's metaanalysis of the selected published studies showed a consistent and substantial treatment effect for antibiotics. However, these studies had mixed HAP/VAP populations in various proportions (largely VAP) and other design issues which may have blunted the treatment response.

Given that the 29% estimate of treatment effect is based on the lower bound of the 95% confidence interval of the estimated treatment effect and that many other factors outlined are likely to make this treatment effect even larger, we believe that the full treatment benefit is likely to be substantially higher than 20%. In addition, we strongly believe that M2 should not have an automatic arbitrary discounting by 50% of M1, but should be based on clinical reasoning and acceptability.

We appreciate the opportunity to provide these comments on the draft guidance on HABP/VABP and thank you in advance for your consideration of these comments as you finalize the guidance.

Sincerely,

Michael Garvin

Michael Garvin, Pharm.D.

Additional Comments

Lines 23, 68, 130, etc: It is unclear why there is no mention of MSSA as a pathogen. MSSA is just as likely to be a pathogen as MRSA. In the telavancin studies, designed to enroll patients with gram-positive pathogens, MSSA was recovered in 31% of patients compared with 48% of patients having MRSA. In the subset of patients with VAP, while the relative proportion of patients with MRSA was higher, there were still substantial numbers of patients with MSSA. This was also true in the linezolid registrational study.[1] More recently, a prospective multinational study of nosocomial pneumonia in ICU patients found a higher incidence of MSSA in patients with VAP with more non-ventilated patients having MRSA.[2] It is suggested that MSSA be included as a pathogen, throughout.

Lines 47, 121, 248: Reference is made to exclusion of patients from chronic care facilities and requirement for 48 hours in hospital prior to enrollment. Patients from chronic-care facilities may present with HABP on admission/transfer to the hospital. These chronic-care environments are akin to a hospitalized setting. The pathogens in these patients are not distinct from those obtained in patients with HABP (although proportions of certain pathogens can vary). Reconsideration for such patients' inclusion in these studies (with allowance for their enrollment into the study even if not hospitalized for 48 hours in the current hospital) would significantly improve the feasibility of such studies, especially if the investigational agent (and comparator) is broadly active. However, if the Agency insists on exclusion of patients with pneumonia associated with chronic health care facilities based on potential difference of bacterial etiologies compared with HABP/VABP, it is unclear how such patients should be studied as they also seem to be excluded from the CABP guideline.

Line 65: Reference is made to the term, "hospital acquired bacterial pneumonia" and "ventilator-associated bacterial pneumonia." Fundamentally, the change in terminology from "nosocomial pneumonia" or "HAP/VAP" to "HABP/VABP" should be endorsed by the IDSA/ATS prior to its incorporation in this guidance. Additionally, FDA should carefully consider and disclose the implication of this terminology change to all currently approved agents with a HAP/VAP claim in the US.

Line 144: Because of the low incidence rate of HAP/VAP in pediatrics, we wish to emphasize the importance of being able to extrapolate adult efficacy data to children.

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[1] Rubinstein E et al. Linezolid (PNU-100766) versus vancomycin in the treatment of hospitalized patients with nosocomial pneumonia: a randomized, double-blind, multicenter study. Clin Infect Dis 2001;32:402-12.

[2] Esperatti M et al. Nosocomial Pneumonia in the Intensive Care Unit Acquired by Mechanically Ventilated versus Nonventilated Patients. Am J Resp Crit Care Med 2010;182:1533-39.

Line 175: Reference is made to the need for studying HABP and VABP separately. The Agency has provided no rationale as to why patients with either HABP or VABP cannot be included in the same study. Reference is also made to the need for study where HABP/VABP is the sole indication. Ordinarily, enrollment of patients into HABP/VABP trials is very challenging. The expectation for two adequate and well-controlled studies would likely be extremely difficult to achieve. We strongly recommend that the Agency consider a single study of reasonable size that enrolls both populations of patients. Indeed, if the Agency insists on ACM as the primary efficacy endpoint in the guidance, then evidentiary standard based on replication of studies becomes unnecessary. We believe both populations of pneumonia patients could be potentially enrolled in the same study; this could be done by stratifying based on presence of HABP or VABP at study entry. In addition, the FDA seems more willing to extrapolate VABP data to cover an indication in HABP (two trials in VABP will support an indication for both HABP and VABP but two trials in HABP will only support an indication for HABP). The rationale for this is not clear. The FDA suggests that confirmation of a bacterial pathogen is more likely in VABP. While we have noted elsewhere that limiting the primary analysis population to MITT excludes many patients with true bacterial pneumonia, we wish to add that if the FDA insists on this primary analysis population, it seems there is little, if any, relevance for this difference between HABP and VABP populations. FDA needs to be more explicit as to the basis for their recommendation.

Line 192: The draft guidance expects the protocol to specify "appropriate objective criteria that allow for the IV to oral switch..." It is unclear what the Agency considers "objective criteria": normalization of all or a combination of WBC, fever, or paO2?

Line 208: Reference is made to following all AEs to resolution. This requirement for following all AE to resolution seems excessive and not practical. It would be reasonable to limit this monitoring requirement to serious AE within a reasonable timeframe.

Line 211 and Line 215: The guidance expects a "sufficient" number of patients >65 and renal failure and "normal laboratory values should be included with clinical measurements." The Agency's expectations for "sufficient" and "normal laboratory values" are unclear in the guidance.

Line 254: Reference is made to the expectation for a chest radiograph demonstrating a new lesion/infiltrate be consistent with HABP/VABP. The types of chest radiographs permissible should be clearly outlined (e.g., chest X-ray, chest CT, etc.). Alternatively, the phrase "chest radiograph" should be replaced by "imaging studies (e.g., chest x-ray, chest CT scan, etc)".

Line 260: Reference is made to the three clinical findings supportive of diagnosis of HABP/VABP (fever/hypothermia, WBC count elevation, and purulent secretions). However, there is the additional expectation for at least one of four other clinical criteria for HABP and one of two other clinical criteria for VABP. The clinical criteria for this study are in addition to confirmed radiographic criteria and demonstrated microbiological criteria. The proposed set of inclusion criteria contradicts the IDSA/ATS Guidelines, which states: "Requiring all three clinical criteria is

too insensitive and will result in many patients with true pneumonia not receiving therapy."[3] The FDA proposed criteria unnecessarily restrict enrollment of patients with true pneumonia. It is also unclear what value requiring an additional sign or symptom might add. A possible change would be to require two of the three clinical features as stated in IDSA/ATS Guidelines.[4]

Line 292, 301: Reference is made to the various severity scoring systems (CPIS, SOFA, APACHE scores) cited in the draft guidance. We are uncertain why CPIS is singled out as it is as flawed, insensitive, and non-specific as all the others, which have been used in the past. It should be sufficient to use one severity scoring system, without preference for CPIS, APACHE or SOFA. We fail to see a need for more than one scoring system. Moreover, expectation for CPIS of >6 has to be based on the original definition, which included baseline microbiology data. Otherwise, scores will largely be <6, and will exclude many patients with true VABP. Modified CPIS have been used to assess treatment regimens and to attempt to correlate with treatment outcomes, but only the original score[4] has been shown to be correlated with the diagnosis (presence) of VABP.

Line 346: Although cited as an example, the recommended CFU/mL limits are somewhat arbitrary and, as stated elsewhere in our comments, neither qualitative nor quantitative bacteriologic sampling has been shown to enhance diagnostic accuracy and we do not believe they are essential in determining overall treatment effect.

Line 398: Stratification by patient location in the hospital is unnecessary as the information could be readily captured without stratification. In fact, we could argue that it makes more sense to stratify by pre-existing conditions, trauma, burns, prior hospitalization (all of which are proven predictors of response).

Line 412: The draft guidance states that the comparator should be "at the recommended dosage that is FDA-approved..." Sometimes the FDA recommended comparator and/or dosage differ from those recommended in IDSA guidelines or used in clinical practice. Moreover, since trials are often conducted internationally, there is also the need for flexibility in the guidance in order to allow, with appropriate justification, the use of a comparator and/or dose, which is acceptable globally. FDA should provide clarity on how sponsors should address the issue of comparators in future trials.

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[3] American Thoracic Society. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. *American Journal of Respiratory and Critical Care Medicine* Vol 171. pp. 388-416, (2005)

[4] Pugin, J et al. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. Am. Rev. Respir. Dis. 1991;143: 1121-1129

Line 431: Reference is made to concomitant antibiotic use for possible pathogens not covered by the investigational agent/comparator. The Guidance should better define how patients with polymicrobial infections who received empirical or targeted therapy with other concomitant antibacterial agents get evaluated in the MITT population. Some further comment as to how/if certain concomitant agents get standardized within the study to cover specific pathogens not covered by investigational agents (e.g., vancomycin for MRSA) should be highlighted in this Guidance. We raise the issue of polymicrobial infections again under Line 625.

Line 485: Administration of antibiotics for another infection outside of respiratory tract (anytime up to 28 days) should NOT automatically constitute clinical progression but rather the potential impact of such antibiotic use should be considered on a case-by-case basis.

Line 518: Reference is made to superiority trials for HABP/VABP with multi-drug resistant (MDR) organisms. There is an assumption here that patients can be easily enrolled to demonstrate superiority based on a primary endpoint of ACM. How feasible would it be to enroll sufficient numbers to demonstrate superiority based on the three suggested study designs? Design #3 will be particularly difficult to demonstrate superiority if, truly, there is clinical equipoise for the selected study doses. The concept of additional therapy on the basis of appropriate background therapy (scenario #2) results in an adjunctive treatment design which is unlikely to lead to demonstrable superiority. Indeed, as currently written in the draft guidance, we have trouble understanding the three proposals for superiority trials and would ask for more detailed explanations regarding how the suggested designs would be implemented.

Line 625: FDA defines the MITT population (which is the primary analysis population) as ITT subjects with a "baseline pathogen... against which the investigational drug has antibacterial activity." We request that FDA clarify whether this population includes polymicrobial infections with at least one pathogen that is not susceptible to the investigational drug.

Line 670: (Sample size): Given FDA's specification of alpha and delta, the Guidance should provide the approximate sample sizes at 80% and 90% power to assist the non-statistical user of the guidance. Such sample size estimation needs to take into consideration the fact that the primary analysis population would be a subset of the ITT population.

Line 765: Reference is made to historical data from prior HABP/VABP studies. We recommend that the FDA include any available data in this Appendix that might shed additional information on the ACM in certain key subgroups (i.e., ACM by patient age, ACM by APACHE II score, ACM by pathogen). This could help better refine the ACM of 20%.

Line 910: Mortality was not the endpoint for the trials reported in Table 2. Three of the 5 trials used to estimated mortality rates for active controls did not report the mortality follow-up time[5] or used time windows[6,7]. Therefore, these studies do not provide precise estimates of 28-day mortality for developing a 28-day mortality margin.

The mortality estimates in Table 2 are based on 7 different active control combinations. This methodology assumes no difference among the different antibiotic treatment strategies. This assumption was not justified in the guidance.

Unlike the studies used to estimate mortality rates for inadequately treated patients in Table 1 (which were almost entirely based on VAP subjects), Table 2 uses data from studies which combined HABP and VABP subjects. Since the guidance differentiates between HABP and VABP, it is not logical to use a combination of patients with both types of conditions to develop the estimate of 28-day mortality separately for both HABP and VABP.

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[5] 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.

[6] 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.

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

27 February 2011

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Food and Drug Administration
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5630 Fishers Lane, Room 1061
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Docket ID: FDA-2010-D-0589

RE: Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment, Revision 1 November 2010

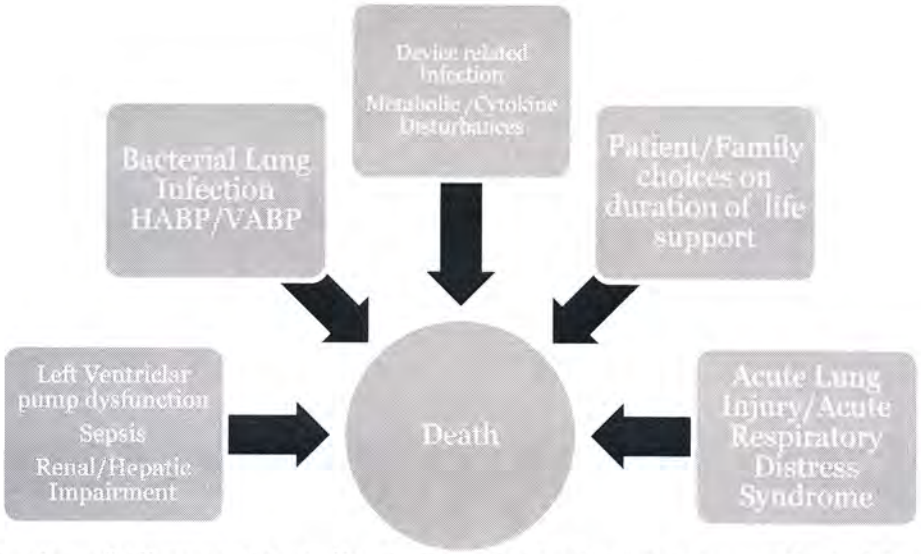
Dear Dr. Toerner,

The opportunity to comment on the guidance is appreciated. The Center for Drug Evaluation and Research (CDER) has performed an extraordinary job in developing the data driven Guidance, with careful and thoughtful public and professional society input since the release of the last guidance for Nosocomial Pneumonia in July 1998.

1. What outcome measures (end points) should be used to distinguish effective from ineffective drugs in a clinical trial for HABP/VAPB?

The recommendation to use mortality is a valuable one. In *chronic* diseases, mortality may be logically linked more directly to an antecedent chronic disease process (i.e., mortality or composite outcomes that includes mortality for cardiovascular disease or cancer). In the case of HABP/VAPB, *acute* lung infection related mortality is accompanied by *rapidly acting* mortality modifying co-morbid conditions such as surgical interventions, catheter and other device related infections, cancer, cardiovascular and metabolic disease modifiers and perhaps doctor patient and family decisions on the continuation of care, within the relatively brief 28 days after start of treatment as proposed in the Guidance.

Regarding the link between intervention for HABP/VABP and death, Katherine Laessig observed[i]: "Mortality, although not difficult to define, is not a clean end point, because determining attributability is in the eye of the beholder and may be unclear even when an autopsy is performed. All-cause mortality may be related to underlying co-morbidities and gives a false impression that, somehow, the antibacterial treatment is related to the deaths." There is reasonable uncertainty to the timing selected for assessment of the primary outcome measure – death. Katherine Laessig further observed, "Of the 23 studies used in the analysis by Sorbello *et al.*, more than half did not specify when the mortality end point was assessed, and a few used 28–32 days as the time of assessment."



Attribution of All-cause Mortality In The 28 Day Post-treatment Period for an Antibacterial for Ventilator-associated Bacterial Pneumonia May Require Careful Evaluation.[ii] *Although patients with high risk of fatality may be excluded at baseline, occurrence of major organ dysfunction in the trial patient population may be linked to risk fatality above and beyond the benefit of appropriate anti-bacterial intervention.*

An alternative assessment of the link between death and VABP is provided by Muscedere and colleagues:[iii] "In a meta-analysis using a random effects model, of the 7 trials that reported hospital mortality, the effect on attributable mortality disappeared with an OR for hospital mortality of 1.03 (95% CI, 0.89–1.21). The aggregate mortality among patients without VAP was 31%, with an absolute attributable mortality of VAP of 1.1% (95% CI, 2%–5%). The heterogeneity was less (I^2, 12%; 95% CI, 0%–74%). On analysis of the 4 studies that reported on trauma patients, the aggregate overall mortality among patients without VAP was 19%. There was little attributable mortality of VAP (OR 1.28; [95% CI, 0.7–2.33]; I2, 48% [95% CI, 0%–83%]) and an absolute attributable mortality of 4% (95% CI, 6%–14%)."

Interventions that result in observable reduction in pneumonia in patients on mechanical ventilation, do not appear to have strong effect on mortality. Examples include endotracheal tubes that permit suction of subglottic secretions[iv] and silver coated endotracheal tubes.[v]

The observations about the limitations of the available investigations may is linked to the variations in study designs, outcome measures, intervention assessments, sample sizes and thoroughness of data collection.

The suggestion has been made to consider duration of resource utilization use, such as mechanical ventilation, as an outcome measure for VABP.[vi]

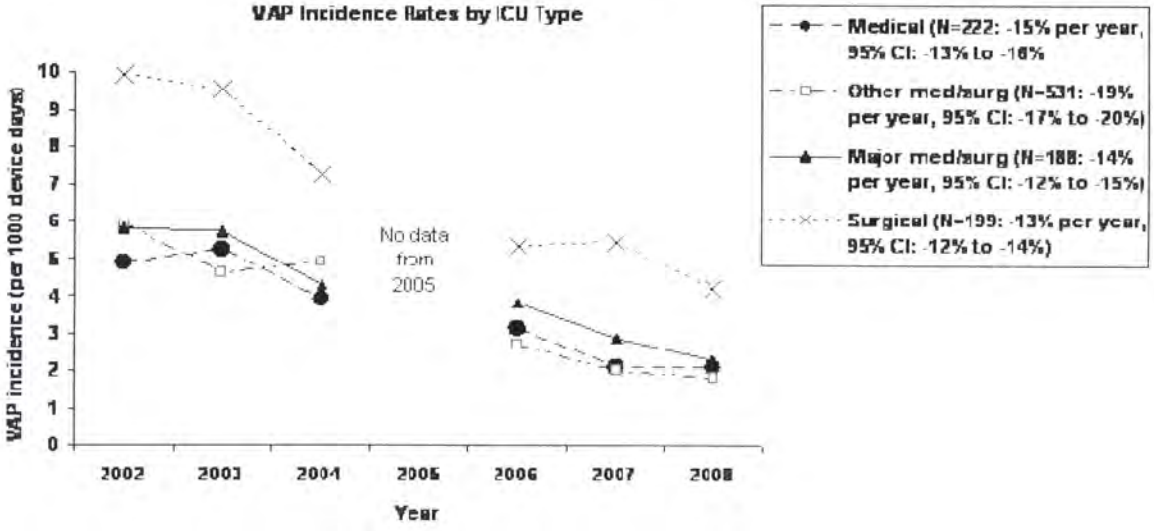
2. Advances in implementation of medical science and administrative changes in the delivery of care of patients may impact (confound) the concepts carefully developed in the Guidance regarding VABP

The recommendations by the Institute of Healthcare Improvement, the American Hospital Association, and the Society for Healthcare Epidemiology of America to prevent VABP by a standard set of prevention maneuvers (ventilator bundle) such as elevation of the head of the bed, daily sedative interruption to assess of readiness to extubate, and daily oral care with

chlorhexidine appear to have had an impact on the incidence of VABP. In addition, identification of VABP as a preventable infection and notification of occurrence of VABP to hospital quality monitors has made the made diagnostic criteria for VABP more rigorous and possibly more difficult to report.

A report from the Mayo Clinic in 2006 commented that "The rate of VABP per 1000 ventilator days decreased from 6 to 0.72 per 1000 ventilator days with implementation of the ventilator bundle.[vii] The American Hospital Association in 2006 reported a 75% reduction in VABP and 14 sampled hospitals reported no cases in a nine month period. [viii] Canadian hospitals have also reported a significant drop in the incidence of VABP.[ix]

National Healthcare Safety Network (NHSN) data summary for 2006 through 2007, issued November 2008, reported a reduction to 2.3 cases of VABP per 1000 ventilator days in a sample of medical surgical units in 187 institutions. The report estimated that about 40% of the reported cases would meet a more rigorous definition of VABP that require a positive culture; thus, the overall incidence density of VABP may be estimated be 2/1000 ventilator days or less. [x]



Abstract 404 SS Magill, JR Edwards, SK Fridkin, Ventilator-Associated Pneumonia in the National Nosocomial Infections Surveillance System and the National Healthcare Safety Network: Analysis of Incidence and Pathogen Distribution, 2002-2008
Presented at the International Conference on Healthcare-Associated Infections, March 18-22, 2010.
http://shea.confex.com/shea/2010/webprogram/Paper1745.html
(Accessed 24 February, 2011)

3. Consideration for sample sizes and availability of patients

Given that the Division of Anti-infective Drug Products recommends mortality as the primary outcome measure in a patient population with an estimated mortality of 20%, exploratory estimates of non-inferiority study sample sizes provided indicate that about 1100-1400 patients with microbiologic diagnosis per treatment group may be needed.[xi]

Exploratory estimation of study feasibility and design in an environment of lowering VABP event rates may be illustrative.
Abt Associates in Cambridge, Massachusetts (1988) on the behalf of the American College of Physicians, American Thoracic Society and Society of Critical Care Medicine estimated about

6000 critical care beds in the United States.[xii] In an optimistic scenario that 10% of the ICU beds are available for a VAP study, 219,000 (600 critical care beds x 365 day/year) critical care bed days would be available per year. From the National Healthcare Safety Network 2008 publication, approximately 35% of the ventilated patients would have VABP.[xiii] The cases of VABP available for screening and consent in an investigation program would be a low 153 patients with VABP per year per 600 beds (0.35 x 219,000 = 76650 ventilator days/year; 2 VAPB cases/1000 ventilator days x 76650 = 153). Even if these estimates are revised upwards, there is a challenge in recruiting the appropriate patient population for clinical investigations.

Perhaps an international collaborative group that could undertake the challenge of implementing a protocol that enforces standardized methodology for VAP prevention and infection control ("VAP bundle"), diagnosis[xiv], exclusion of prior antibacterial agents, management of ventilator associated tracheobronchitis, GCP and microbiology specimen processing and thus be successful over 2 or more years in completing two studies.

Implication of the changed standard of care on the constancy assumptions (i.e. do we have reliable data that a comparator drug's treatment effect would not differ between studies conducted today and studies conducted previously?) and assay sensitivity assumptions (i.e., do we have reliable assumptions about treatment effect size and the ability of the clinical investigations to distinguish between effective and ineffective treatments given the changes in standard of supportive care?) should be considered. [xv]

4. *Considerations for difficult to treat bacteria*

The more problematic pathogens in HABP/VABP may be the multidrug resistant or metallo-β-lactamase producing Gram negative bacteria. Such bacteria may be a relatively small percentage of isolates. The Guidance does provide some help (line 506).

Some provision needs to be made in the Guidance to encourage pathways to develop drugs indicated for the most highly resistant Gram negative pathogens for the HABP/VABP indications. Until point of care rapid diagnostic tests useful for pathogens of interest are available and allow enrollment of patients at the point of randomization, the resistant pathogens will be a subset of the total pathogen population. The proposed guideline requires the presence of confirmed microbiologic diagnosis at baseline; therefore, some estimate of the minimum number of the subset of multidrug resistant Gram negative bacteria and their numerical response rate relative to the overall response rate in an investigation plan could be discussed. Lead time for the approval of new treatments can be long; therefore, some points to consider for investigations of the more resistant bacteria as a subset in severely ill patient will be helpful.

Sincerely,

Roomi Nusrat

Roomi Nusrat, MD

[i] KA Laessig, End Points in Hospital-Acquired Pneumonia and/or Ventilator-Associated Pneumonia Clinical Trials: Food and Drug Administration Perspective, Clin Infect Dis. (2010) 51(Supplement 1): S117-S119.
[ii] Nusrat, Transcript for Issues in the Design and Conduct of Clinical Trials for Antibacterial Drug Development; Public Workshop, August 2, 2010, pdf page 309 (Accessed 24 February 2011)
http://www.fda.gov/Drugs/NewsEvents/ucm211165.htm
O Gajic, B Afessa, BT Thompson *et al.*, Prediction of death and prolonged mechanical ventilation in acute lung injury, Critical Care 2007, 11. Available online http://ccforum.com/content/11/3/R53.
II Siempos, KZ Vardakas, C. Kyriakopoulos *et al.*, Predictors of Mortality In Adult Patients With Ventilator-associated Pneumonia: A Meta-Analysis, Shock, Vol. 33, No. 6, pp. 590-601, 2010.
Once lung injury advances to criteria of Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS), as defined according to the American-European Consensus conference, the advanced derangement of lung function may be associated with mortality that would not necessarily benefit from anti-bacterial therapy.
[iii] JG Muscedere, A Day, and DK Heyland, Mortality, Attributable Mortality, and Clinical Events as End Points for Clinical Trials of Ventilator-Associated Pneumonia and Hospital-Acquired Pneumonia, Clin Infect Dis. (2010) 51 (Supplement 1): S120-S125.
[iv] TaperGuardMT Endotracheal Tubes and TaperGuard EvacTM Endotracheal Tube, Special 510(k) Summary, Center for Devices and Radiological Health, Food and Drug Administration, April 3, 2009.
http://www.accessdata.fda.gov/cdrh_docs/pdf9/K090352.pdf (Accessed 24 February, 2011)
[v] Agento™ I.C.®DSilver-Coated Endotracheal Tube (Intermediate High Volume Low Pressure), 510 (k) Summary, Center for Devices and Radiological Health, Food and Drug Adminstration, March 25, 2008.
http://www.accessdata.fda.gov/cdrh_docs/pdf8/K080170.pdf (Accessed 24 February, 2011)
MH Kollef, B Afessa, A Anzueto *et al.*, Silver-Coated Endotracheal Tubes and Incidence of Ventilator-Associated Pneumonia, JAMA. 2008; 300(7):805-813.

[vi] Muscedere op. cit., p. S122.
[vii] CD Burger and RK Resar, "Ventilator Bundle" Approach to Prevention of Ventilator-Associated Pneumonia, Mayo Clin Proc June 2006; 81(6):849-850.

[viii] American Hospital Association Quality Advisory, March 20, 2006.
http://www.aha.org/aha/advisory/2006/061120-quality-adv.pdf (accessed 24 February 2011)
[ix] Ottawa Hospital, New Cases of Ventilator Associated Pneumonia, July 2010.
http://www.ottawahospital.on.ca/wps/wcm/connect/e2b19880453979549 1bcb1eabb1d6a47/vap-rates-e.pdf?MOD=AJPERES (accessed 24 February 2011)
[x] JR. Edwards, KD Peterson, ML Andrus, *et al.*, Am J Infect Control 2008; 36:609-26.
[xi] Muscedere op. cit. p. S124.
[xii] R Schmitz, M Lantin, A White, Future Needs in Pulmonary and Critical Care Medicine. Cambridge, Mass: Abt Associates; 1998.
[xiii] JR Edwards op. cit. p. 615.
[xiv]
1. M Klompas, Does This Patient Have Ventilator-Associated Pneumonia? JAMA. 2007;297:1583-1593.
2. AM Lilienfeld, B Kordan, A study of Variability of Interpretation of Chest X-Rays in the Detection of Cancer, Cancer Research 26, 2145-2147, 1966.
3. T Cherian, EK Mulholland, JB Carline *et al.*, Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies, Bulletin of the World Health Organization 2005;83:353-359.
Donald E. Craven and Karin I. Hjalmarson, Clin Infect Dis (2010) 51(Supplement 1): S59-S66
The inter-observer agreement of chest x-ray findings is reported to be low, particularly when it comes to agreement on new positive findings.

In the WHO study cited, a reference categorized 43% of 208 chest x-rays as showing alveolar consolidation or pleural effusion (primary end-point pneumonia); the proportion thus categorized by each of the 20 test readers ranged from 8% to 61%.

Patients in the intensive care unit prior to intubation may have an abnormal chest x-ray. In this group of patients with a prior abnormal chest x-ray, the ability of diagnose a new pneumonia radiographically has particular limitations. In some cases what is considered a new pneumonia may be a case of tracheobronchitis.

[xv] It is believed that Socrates at the Oracle of Delphi when asked what the definitions of knowledge and wisdom were, responded by saying, "That which I do not know, I know that I do not know."

24 February 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
Docket No. FDA-2010-D-0589
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Dear Sir or Madam:

On behalf of Johnson & Johnson Pharmaceutical Research & Development, L.L.C., I am providing the following recommendations and comments with regard to the FDA draft guidance entitled, "Guidance for Industry, Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment", dated November 2010.

This guidance, when finalized, has the potential to be a valuable tool for Sponsors who are considering developing antibacterial agents for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP).

Overall Comments

Resistance to antibacterial agents is on the rise around the world, and therefore, the FDA and drug sponsors have a shared interest in ensuring the standards established for clinical testing and approval of these important products are reasonable and meaningful, so new molecular entities can continue to be developed to treat serious infections. Within this draft guidance document, the FDA notes their current thinking has evolved regarding the overall development program and clinical trial designs for drugs to support an indication for treatment of HABP and VABP and this guidance reflects their current views that take into consideration discussions that have occurred at recent HABP/VABP workshops. We thank the Agency for providing much needed clarity in terms of their expectations of performing non-inferiority (NI) and superiority studies in HABP/VABP patients, including defining the trial population, identifying a single primary analysis population (MITT), clearly stating the recommended primary endpoint, and defining the NI margin. However, based on our recent experience conducting several studies in HABP/VABP patients we believe the new primary endpoint of all-cause mortality and the proposed inclusion and exclusion criteria will significantly impact the feasibility of conducting such trials in a timely manner, and will likely limit the development of important new antibacterial therapies for treating these serious and life-threatening infections. Before this guidance is finalized, we believe the current draft guidance can be further enhanced by continuing

discussions with clinicians, medical societies and industry to ensure study requirements are feasible and aligned with current standards of clinical practice and that study size requirements are reasonable given the relatively limited patient population in the United States and worldwide.

Our concerns regarding the feasibility of conducting studies that adhere to the recommendations in this guidance are based on our recent experience conducting several studies in HABP/VABP patients and more specifically the challenges we are encountering with recruitment into an ongoing Phase 3 study in patients with VABP (DORI-NOS-3008). Study DORI-NOS-3008 is a double blind, randomized, multi-center comparator controlled Phase 3 safety and efficacy study that implements many of the principles proposed in this draft guidance document. Eligible patients must be hospitalized for at least 5 days, on mechanical ventilation for ≥48 hours, have a chest radiograph consistent with pneumonia, have a fever/hypothermia or WBC count indicative of systemic infection, have a CPIS ≥6, an APACHE II Score >8 and <35, and a bronchoalveolar lavage (BAL) or mini-BAL performed at baseline from which at least one bacterial pathogen must be isolated from culture at $\geq 10^4$ CFU/mL. Patients are excluded if they receive >24 hours of prior antibiotic therapy (before the first dose of study drug) for the current episode of VAP. The use of adjunctive aminoglycoside therapy is only permitted at initiation of study drug therapy as empiric adjunctive therapy for infections suspected to be caused by a carbapenem-resistant gram negative pathogen. The adjunctive aminoglycoside must be discontinued by 72 hours unless a pathogen is isolated from the baseline lower respiratory tract (LRT) specimen that is resistant to the comparator, and presumably the investigational agent also. The first patient was enrolled into this study April 1, 2008 and as of February 15, 2011 only 272 patients have been enrolled (approximately 100 pts/year). A total of 128 sites have been initiated and had study drug shipped. However 89 sites have been closed due to lack of enrollment. Of the 39 sites that remain open, only 22 sites recruited 1 or more subjects in 2010. Given the enrollment challenges, the feasibility of completing this study and providing data in a relevant timeframe is currently under evaluation. In addition, given the very sick and complex patient population, the limited number of patients with VABP, the small numbers of patients enrolled per site, and the complexity of study design, there are very high costs per patient enrolled into these trials (much higher than costs we are aware of in other indications). Therefore, the feasibility of recovering the costs for conducting this and future HABP/VABP studies is low, and potentially warrants re-assessment of the feasibility of initiating development programs for new antibacterial agents.

Specific Comments

Lines 20 - 25 and multiple area throughout the guidance document

It is not clear whether the FDA is suggesting that the etiologic pathogens of HABP/VABP that would be recognized by the Agency are limited to MRSA, *Klebsiella pneumoniae,* and (*Pseudomonas aeruginosa* and *Acinetobacter* species) or if other pathogens which occur in HABP/VABP, such as MSSA, all Enterobacteriaceae, *S. pneumoniae* and *H. Influenzae,* would also be considered target pathogens if isolated from qualified respiratory specimens and grow at or above a pre-specified minimal quantitative threshold. We recommend that the list of target pathogens not be limited to MRSA, *Klebsiella pneumoniae,* and Gram-negative non-

Enterobacteriaceae (*Pseudomonas aeruginosa* and *Acinetobacter* species) and the FDA allow and clarify within the guidance document that all pathogens isolated from a qualified respiratory specimen that grow at or above a pre-specified quantitative threshold be considered etiologic pathogens of HABP/VABP and may qualify subjects to be included in the primary MITT analysis set.

Lines 121 - 125 and Footnote 10

Given the statement, "Pneumonia that occurs in persons residing in chronic care facilities is not considered to be HABP because the bacterial pathogens in such patients are less likely to be similar to bacterial pathogens in patients with HABP/VABP," and given footnote 10 only discusses the different rates that pseudomonas was isolated in subjects with VABP versus health-care associated pneumonia, it is not clear whether the FDA is expecting that a minimum proportion of subjects enrolled in a trial be infected with pseudomonas. Although it may be desirable for some studies to enrich enrollment of subjects with a specific pathogen(s), it may not be practical or reasonable to accurately predict a specific pathogen prevalence in order to aide enrichment into a HABP/ VABP trial. Therefore we recommend not expecting a minimum proportion of subjects be infected with any specific pathogen and that it be clearly noted in the guidance document that all pathogens isolated from a qualified respiratory specimen that grow at or above a pre-specified quantitative threshold be considered etiologic pathogens of HABP/VABP.

Line 198

We would not choose all-cause mortality as the primary endpoint because it is an indirect and diluted measure of antibiotic effect. HABP/VABP is often an indicator of severity of overall illness and is associated with an increased risk of death. However, curing pneumonia may not prevent the patient from dying. Furthermore, mortality due only to HABP/VABP is difficult to discern and too small of a population to use as a study endpoint. Therefore, we recommend other endpoints, such as clinical cure, be further explored as the primary endpoint instead of all-cause mortality.

Lines 233 – 235

We are not aware of any available methods or scoring systems to assess risk of death caused by HABP/VABP and therefore assume the guidance is recommending to enroll subjects with an approximately 20% or greater risk of all-cause mortality. However, scoring systems to assess all-cause mortality generally do not take into consideration the presence or absence of pneumonia. Therefore, it is not clear how enrolling subjects with an approximately 20% or greater risk of all-cause mortality regardless of the presence or absence of pneumonia will inform the role of antimicrobials in treating subjects with HABP/VABP. We recommend that the FDA chose a more meaningful endpoint that is likely to measure the role of antimicrobials in treating these subjects; for example, clinical cure based on assessment of signs and symptoms of pneumonia.

Lines 244 - 362

Given the Agency proposes a high bar to define pneumonia by requiring a minimum threshold for bacterial colony counts from respiratory specimens obtained by invasive methods (i.e., $\geq 10^3$ CFU/mL from a protected brush specimen [PBS] and $\geq 10^6$ CFU/mL from an endotracheal tube [ET] specimen), we recommend that the other

more controversial study entry criteria be relaxed (see comments on Line 254 regarding baseline chest radiographs) or removed (see comments on Lines 292-293 and Footnote 12 regarding CPIS and on Line 375 regarding prior antibiotic therapy).

Line 254

Given double-blind studies are recommended, and a high bar is proposed as a minimum threshold for bacterial colony counts from respiratory specimens obtained by invasive methods (i.e. $\geq 10^3$ CFU/mL from a PBS and $\geq 10^6$ CFU/mL from an ET specimen), we propose any qualified medical professional, including the principal investigator (who is blinded to treatment assignment), may provide a written report of the baseline chest radiograph. We also note, in our recent experience conducting HABP/VABP studies, many principal investigators are pulmonologists or intensivists (ICU physicians) who are experienced with and often the only physicians in the hospital who interpret chest radiographs of patients in the ICU.

Lines 292 - 293 and Footnote 12

Given a high bar is proposed to define pneumonia by requiring a minimum threshold for bacterial colony counts from respiratory specimens obtained by invasive methods (i.e. $\geq 10^3$ CFU/mL from a PBS and $\geq 10^6$ CFU/mL from an ET specimen), we suggest removing CPIS as a required inclusion criterion. The CPIS methods referenced in footnote 12 (Pugin and Singh) that use a CPIS >6 as suggestive of pneumonia require the baseline respiratory specimen culture results be available at the time the score is calculated. However, these culture results are not generally available at the time a patient is being screened for enrollment into a clinical trial. Therefore, implementing a Pugin or Singh CPIS system is often not possible. If the FDA is not amenable to removing CPIS as an inclusion criterion, alternative CPIS methods that do not require culture results (Luna for example) and a score appropriate for that system (CPIS >5 for the Luna method for example) should be allowed.

Lines 313 - 333

Further guidance is requested to clarify subject eligibility for the MITT analysis set when results from multiple specimen types (i.e. blood, tracheal aspirate (TA), protected brush specimen (PBS), bronchoalveolar lavage (BAL), mini-BAL) are available. Specifically, we recommend the following changes for assessing patients who meet the following scenarios:

1. If a LRT specimen (i.e., TA) fails the microscopic examination test (SEC >10), a pathogen(s) isolated from other qualified LRT specimens (i.e., mini-BAL with SEC <10) is allowed.

2. If none of the LRT specimens pass the microscopic test, a pathogen isolated from the blood are allowed if other sources for bacteremia are not suspected (e.g. Gram positive organisms isolated from line tip cultures and Gram negative organisms isolated from subjects with a urinary tract infection)

Lines 317 - 320

Please clarify whether "sent to the laboratory..." refers to the local microbiology laboratory, the central laboratory, or either laboratory. Given the short transit time required to deliver the specimens to the laboratory for Gram stain and culture (2 hours

at room temperature and ≤24 hours with refrigeration), specimens are traditionally sent to the site local microbiology laboratory. We propose that the Gram stain results obtained by the local lab be used for determination of specimen acceptability for the analysis population. As such, we suggest the guidance be revised and propose the following:

At the time of enrollment before administration of clinical trial antimicrobial therapy, an adequate specimen of respiratory secretions should be obtained from all patients and sent to the **site's local microbiology** laboratory for Gram stain and culture with in vitro antibacterial susceptibility testing performed on appropriate organisms isolated from the specimen.

Lines 326 – 329
The specimens from "endotracheal suction" should be further clarified in the guidance document to remove ambiguity. We suggest the guidance be revised propose the following:

Specimens obtained from bronchial brush, ~~**or**~~ endotracheal suction, **BAL and mini-BAL** (VABP trials) generally should be appropriate for inclusion in evaluation of respiratory culture results (e.g., fewer than 10 squamous epithelial cells)

Lines 335 – 340
We believe non-bronchoscopic methods for obtaining a LRT specimen should be allowed as an acceptable modality for collecting LRT specimens since it is a more commonly performed at some institutions and is considered a reliable sampling method. As such, we suggest the guidance be revised and propose the following:

An appropriate lower respiratory tract specimen can be obtained by any of the following modalities:

- Deep expectoration
- Endotracheal aspiration in intubated patients
- **Mini-BAL or** bronchoscopy with bronchoalveolar lavage or protected-brush sampling

Lines 345 – 349
It is not clear if the criteria defining threshold bacterial counts for the multiple specimen types listed in the guidance document are meant to be definitive or if other values described in the literature may be used. For example, some literature supports bacterial counts of $\geq 10^4$ CFU/ml in the BAL and mini-BAL, $\geq 10^5$ CFU/ml in TA, and $\geq 10^6$ CFU/ml in sputa as correlating with lower respiratory tract infections. We recommend that the guidance reflect the allowance of these specimen types and propose the guidance be revised to read as follows:

The protocol should characterize the microbiological findings based on the type of specimen collection. For example, colony counts of 10^3 colony forming units/ml (CFU/ml) can be considered a threshold for identifying pathologic bacteria from protected brush specimen**; colony counts of 10^4 CFU/ml can be considered a threshold for identifying pathologic bacteria from BAL and mini-BAL; colony**

counts of 10^5 CFU/ml can be considered a threshold for identifying pathologic bacteria from tracheal aspiration; whereas colony counts of 10^6 CFU/ml can be considered a threshold for identifying pathologic bacteria from ~~**an endotracheal tube**~~ **a sputum** specimen

Lines 345 – 349
Further guidance is requested to clarify how to classify culture results for patients who have multiple specimen types from the blood or LRT (TA, PBS, BAL, mini-BAL) that are eligible for inclusion in the MITT analysis population. We recommend the following:

1. All bacteria isolated from all LRT specimens that meet microscopic examination criteria and grow at the minimal threshold criterion be considered a pathologic bacteria.

2. If none of the pathogens from the LRT specimens meet the prespecified minimum acceptable quantitative threshold, the blood pathogens would still allow inclusion into the MITT analysis population.

Lines 351 – 353
Since definitive in vitro susceptibility testing is traditionally performed at the central laboratory, we recommend this be specified in the guidance document. As such, we propose the guidance be revised as follows:

Definitive in vitro susceptibility testing should be performed **at the central laboratory** on all isolates to the test drug, the comparator drug, and other antibacterial drugs that may be used to treat HABP/VABP caused by the targeted pathogens.

Line 375
Given this guidance sets a high bar to define pneumonia by requiring a minimum threshold bacterial colony counts from respiratory specimens obtained by invasive methods (i.e. $\geq 10^3$ CFU/mL from a PBS and $\geq 10^6$ CFU/mL from an ET specimen), we propose that any patient who provides a respiratory specimen that meets this standard be allowed to enroll into the study, regardless of the receipt of any amount of antibacterial therapy in the days or month prior to enrollment. We note that prior receipt of effective antimicrobial therapy should significantly reduce the likelihood that a respiratory specimen meets the minimum threshold criteria. We also note that prior receipt of any antibacterial therapy (effective or ineffective) increases the risk that the patient will be infected with a less susceptible and often more difficult to treat pathogen. Therefore the receipt of prior antibacterial therapy should not compromise the ability to assess the efficacy of the investigational agent. Furthermore, given this guidance restricts enrollment to patients who are more likely to receive prior antibiotics because they are required to have been hospitalized for at least 48 hours and have sufficiently severe illness to be associated with ≥20% mortality, further excluding such patients who have also received prior antibiotics within the past 30 days with activity against bacterial pathogens that cause HABP/VABP will severely restrict the number of patients who may be eligible to enroll, and significantly decrease the feasibility of conducting trials in patients with HABP/VABP. In our

recent experience conducting 3 Phase 3 HABP/VABP studies 23%, 40% and 72% of patients enrolled in these studies, respectively, received antibiotics within the 72 hours prior to enrollment. If a restriction that excludes any patient who has received antibiotics with activity against bacterial pathogens that cause HABP/VABP within the previous 30 days were required, the number of subjects eligible for enrollment would be significantly reduced and the feasibility of conducting the study would be extremely small. Therefore, we suggest that the criterion regarding prior antibiotic use be removed.

Lines 447 – 454 and Footnote 15

The guidance recommends to de-escalate antibacterial therapy at 48-72 hours. In our recent experience conducting HABP/VABP studies we believe this time limit may be too restrictive for large multi-center trials where it often takes 4 to 5 days for physicians to receive final culture results. Therefore, we suggest expanding the window for de-escalating therapy to 48-96 hours.

In addition, investigators participating in the ongoing Phase 3 study DORI-NOS-3008 (where subjects have a bronchoscopic BAL or mini-BAL performed at baseline from which at least one bacterial pathogen must be isolated from culture at $\geq 10^4$ CFU/mL) request the Sponsor allow investigators to continue administering aminoglycoside to subjects who have at least one non-susceptible bacteria isolated from the LRT that does not meet the minimum threshold bacterial colony counts. Investigators note for these subjects the non-susceptible bacteria may not meet the protocol definition of a qualifying pathogen but continuing aminoglycoside is necessary to comply with standard of care therapy. Therefore, we recommend the guidance allow investigators to continue concomitant therapy in patients who have a susceptible pathogen isolated from an acceptable LRT specimen that grows at the minimal quantitative threshold criterion and at least one non-susceptible pathogen that grows from a specimen that does not meet this criterion.

Lines 462 - 504

There is no mention of eradication of pathogens as an endpoint in section 9 "Efficacy Endpoints", although "The primary analysis population should be patients with a microbiologically confirmed bacterial etiology for HABP/VABP" as stated on page 5 (lines 169 – 171). We suggest the guidance add microbiological outcome as a secondary endpoint and allowance be made to infer microbiological outcome from the clinical response.

Line 490

PRO assessment is excessive and cumbersome in a trial where mortality is the primary endpoint. Furthermore, PRO assessments for secondary endpoints in patients with HABP, and particularly those with VABP, are unlikely to be sensitive to antimicrobial effect given this patient population is often heavily sedated, receiving potent analgesics, and have symptoms that are likely to be confounded by co-morbidities. For these reasons, we recommend not expecting PRO assessments in HABP/VABP trials.

Line 625 – 632
As susceptibility will not have been determined for most investigational agents we suggest the following wording: All randomized patients who have a baseline bacterial pathogen that causes HABP/VABP against which the investigational drug is expected to have antibacterial activity. Furthermore, because the study should be double-blinded but it is desirable to continue the investigational agent whenever possible, and because HABP/VABP is associated with severe morbidity and high mortality and the risks of continuing non-effective therapy are unacceptably high, the guidance should provide allowances for the investigator to be unblinded to randomization assignment but to continue to provide study drug treatment as appropriate (preferably according to a protocol specified algorithm) when patients have a pathogen that is potentially covered by one agent but not the other.

Lines 627 - 628
The guidance defines the MITT population as patients with bacteria pathogens that cause HABP/VABP that have been identified in specimens "including blood or appropriate sputum specimen". We believe it would be helpful to also allow specimens from the BAL or TA to be used, especially in VABP trials. Therefore, we suggest the guidance be revised to reflect the acceptance of pathogens isolated by all allowed methods and suggest the following revisions be made:

... This includes bacterial pathogens associated with HABP/VABP identified in blood or appropriate sputum specimen, **including TA, PBS and BAL, mini-BAL (VABP trials)**.

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Thank you for the opportunity to review and comment on this draft guidance. Should you have any questions or comments, please contact me directly at (908) 927-2449.

Sincerely,
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Samuel D. Maldonado, M.D., MPH, FAAP
Vice-President and Head
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Document Details

Antonio Perez - Comment

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While this guideline emphasizes that antibacterial's efficacy is jeopardized by the increasing resistance of bacteria (lines 22-, 70-), which is aggravated by an aging population and an increasing number of immunosupressed subjects, omits the role of biologicals (e.g. monoclonal antibodies (mAbs)) as adjunctive therapy of HABP/VABP in combination with standard of care, without interfering with antibiotics, due to their different mode of action. The IgG or IgM mAbs' mechanism of action is either by direct targeting to bacterial cell surfaces or neutralizing bacterial virulence factors, which are not affected by the traditional mechanisms of antibiotic resistance, therefore suitable to treat resistant and multidrug resistant pathogens causative of HABP/VABP, and for a prolonged period of time due to their long half life (<100 hours with IgMs and ~21 days with IgGs). The microbiological criteria (line 312-) of mAbs are not yet defined nor traditional PK/PD criteria an be used as mAbs effector functions follow stimulating phagocytosis of bacteria by macrophages, activating the complement cascade, inducing antibody-dependent cellular cytotoxicity (ADCC) by macrophages or complement-dependent cytotoxicity (CDC). Safety considerations (item 6), in terms of age, gender, drug-drug interactions and special populations (renal or liver insufficiency) can be often skip in the clinical development of mAbs. MAbs, given in combination with standard antibiotic therapy can follow the successful clinical history in other therapeutic areas, such as oncology, where survival rates are steadily increasing. Promising results with a mAbs for the treatment of HABP/VABP caused by Pseudomonas aeruginosa may pave the way for their inclusion in this guideline (Lu 2011). References: Lu Q, Rouby JJ, Laterre PF, et al. Pharmacokinetics and Safety of Panobacumab: A Specific Adjunctive Immunotherapy in Critical Patients with Nosocomial Pseudomonas aeruginosa O11 Pneumonia. 2011. In press.

Summary of Comments Submitted to Docket No. FDA-2010-D-0589

Section	Comment
General	• Lack of feasibility of conducting trials. Currently enrolling about 100 patients per year, 128 sites initiated, in a HABP/VABP trial: 89 sites closed due to lack of enrollment • For worldwide studies, need to harmonize protocols; all-cause mortality might not align with regional guidance for HABP/VABP • Reconsider the inclusion of healthcare-associated pneumonia; include an indication for treatment of resistant organisms • International collaborative groups could undertake the challenges of implementing a protocol • Problems with targeting a population expected to have 20% mortality, more unlikely in HABP • Advances in delivery of intensive care has reduced incidence of VAP • 20% or greater mortality unlikely with HABP; in many centers, mortality 10-15%, unless patient displays signs of organ dysfunction associated with sepsis; enhancement of enrollment with more critically ill patients reflects management of organ dysfunction and do not reflect efficacy in HABP/VABP
Trial Populations	• Clarify if only one trial is sufficient, and whether a single trial in VABP will support both VABP and HABP indications • No rationale as to why HABP and VABP should be studied separately; should be able to stratify in same trial; consider a single trial of reasonable size - if all-cause mortality is used, unnecessary to confirm in second trial • Requirement for microbiologic confirmation not consistent with treatment guidelines; makes trial large and infeasible. Primary analysis population should be ITT; micro ITT should be important secondary; uncertainties regarding method of specimen collection and appropriate cut-off values
Clinical Microbiology Considerations	• Recognition of PCR or other nonculture methods of pathogen detection; guidance should better define how patients with polymicrobial infections be evaluated in MITT • Quantitation should not be absolute criteria CFU/ml limits are somewhat arbitrary and not essential; allow mini-BAL • Threshold criteria for sputum and BAL need to be provided

Section	Comment
Entry criteria	• Clarify if patients with tracheobronchitis can be enrolled if they subsequently develop pneumonia
	• CXR not sensitive or specific for diagnosis of pneumonia; CT and MRI more frequently applied; may identify infiltrate not seen on radiograph
	• Fever and ↑WBC are not associated with nosocomial pneumonia, elderly might not have fever; requirement of all three entry criteria would exclude many patients with HAPB/VABP; allow 2 of the 3 criteria for enrollment
	• CPIS score should not be required for VABP; discredited for use in surgical patients. Other scoring systems purely descriptive and not validated for purpose of clinical trial enrollment
Comparators	• Treatment guidelines may no longer be useful in certain intensive care units • FDA-approved for treatment indications overly restrictive, consider use of other antibiotics depending on currently recognized treatment • Dosages used may differ from FDA-approved labeling, allow international flexibility in comparator
Prior antibacterial drug therapy	• Excluding patients who received antibiotic for 30 days prior is unjustified and impractical; allow less than 24h of short acting antibiotic therapy • Surgical and trauma patients often receive perioperative antibiotics or short course therapy for other infections; exposure to these nonstudy antibiotics should not confound efficacy
Efficacy endpoints	• Sole primary endpoint of mortality is an impediment in facilitating clinical development, unfeasible, impractical. Most mortality in severely ill patients is not due to inability to oxygenate and ventilate, but due to other multi-organ dysfunction; mortality due to acute lung infection is hard to ascertain, uncertainty as to timing of outcome at day 28-32 • All-cause mortality is not an outcome of relevance to clinicians. Mortality is difficult to discern and too small of numbers of a population to study as an endpoint. • Patients can be kept artificially alive on a ventilator; alternatively DNR orders allow patients to die earlier; either scenario has nothing to do with efficacy of treatment regimens • All events other than mortality are ignored. Patient who requires modification of initial therapy for either lack of efficacy or adverse events will be judged as success • Consider a clinical endpoint that includes 28-day all cause mortality

Section	Comment
	• Microbiological eradication influences other clinical parameters and is a useful and sensitive marker • Other endpoints: "clinical efficacy", duration of fever, improvement in PaO_2/FiO_2; superiority endpoints such as serial PaO_2/FiO_2, microbiological eradication, duration of therapy, need to modify therapy • PRO's are not realistic; PRO tools do not exist: this is a non-starter for HABP/VABP; PRO excessive and cumbersome, not practical for patients who are likely to be sedated
Statistical Considerations	• Limited generalizability of historical studies to modern trials. Extensive discounting to reach M2 is unclear. Double-discounting is arbitrary, mix of statistical science and arbitrary discounting is unclear. M2 justification at something less than 20% reasonable by clinical judgment, not by arbitrarily discounting M1. NI margin of 12.5-13% equally supportable • Follow-up time to report of mortality outcome was not reported for some studies: no precise estimates for mortality and timing. Guidance should justify the use of different control groups and why the assumption that all would perform similarly. Some studies used combined HABP/VABP, others VABP only • Sample size of about 1100-1400 patients per treatment group is required (total of about 6000 ICU beds in U.S.) • Unclear how 1.67 OR metric obtained for mortality below 20%, clarify how 1.67 was selected (20% mortality, 10% NI margin, test drug as high as 30% mortality = OR 1.71?) • If study protocol prespecified risk difference metric, and mortality observed at less than 20%, guidance should clarify how to handle data review • Address role of sample size re-estimation in light of varying mortality in active control group, type I error rate could exceed 5% based on usual confidence interval approach to noninferiority
Trials in unmet need	• Not feasible to enroll sufficient numbers for superiority. Difficult to demonstrate superiority with design 3. Background therapy is unlikely to demonstrate superiority as in design 2. Guidance should have more detail about how to implement the trial designs • Single comparator drug not feasible; the minimum number of resistant pathogens relative to the overall response rate should be specified