Guidance for Industry

Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

DRAFT GUIDANCE

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

March 2009
Clinical Antimicrobial
Revision 1

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

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Guidance for Industry[1]
Community-Acquired 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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 in the clinical development of drugs for the treatment of community-acquired bacterial pneumonia (CABP). 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 CABP.[2] This guidance is intended to serve as a focus for continued discussions among the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products and pharmaceutical sponsors, the academic community, and the public.[3]

This guidance revises the draft guidance for industry *Community-Acquired Pneumonia — Developing Antimicrobial Drugs for Treatment* published in 1998. Once final, this guidance will be considered the FDA's current thinking regarding the development of drugs for the treatment of CABP. It also supersedes, with regard to the development of drugs to treat CABP, more general guidance issued many years ago (i.e., *Clinical Evaluation of Anti-Infective Drugs (Systemic)* and *Clinical Development and Labeling of Anti-Infective Drug Products*,[4] as well as

[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 purpose of this guidance, all references to *drugs* include both human drugs and therapeutic biological products regulated by CDER 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 antimicrobial drug products.

[4] See http://www.fda.gov/cder/guidance/old047fn.pdf and http://www.fda.gov/cder/guidance/old043fn.pdf, respectively.

the joint FDA/Infectious Disease Society of America's (IDSA's) *General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products*.[5])

For the purpose of this guidance, we assume that the majority of hospitalized patients will be initially treated with intravenous (IV) antibacterials and ambulatory patients will be treated with oral antibacterial drugs. However, this does not preclude the enrollment of hospitalized patients in oral drug trials. Additionally, patients in IV antibacterial trials may need to be enrolled in an emergency room setting to preclude use of prior antibacterial therapies.

This guidance does not address the development of drugs for other purposes or populations, such as treatment of patients with viral infections or atypical bacterial pathogens (e.g., *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*), hospital-acquired pneumonia, or ventilator-associated pneumonia. If sponsors wish to develop drugs with activity against these pathogens, they should discuss the trial designs with the FDA. As the science of this indication evolves and new information accumulates, this guidance may be revised.

This guidance does not contain discussion of the general issues of clinical trial designs or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.[6] This guidance focuses on specific drug development and trial design issues that are unique to the study of CABP.

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

Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality. It is estimated that approximately one million episodes of CAP occur annually in adults 65 years of age and older in the United States. Overall mortality remains relatively high, ranging from 5.1 percent for patients hospitalized or treated in an ambulatory setting to 36.5 percent for patients treated in an intensive care unit.[7] Common etiologic agents of CAP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *M. pneumoniae*. Certain

[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 CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[7] Fine, MJ, MA Smith, CA Carson, SS Mutha, SS Sankey, LA Weissfeld, and W Kapoor, 1996, Prognosis and Outcomes of Patients with Community-Acquired Pneumonia: A Meta-Analysis, JAMA, 275:134-141.

respiratory viruses, and atypical bacterial pathogens such as *C. pneumoniae* and *L. pneumophila*, also cause CAP.

Since the FDA published draft guidance on the development of antimicrobial drugs for the treatment of CAP in 1998, there have been public discussions regarding clinical trial designs to study CAP, including an FDA-IDSA workshop and a meeting of the Anti-Infective Drugs Advisory Committee.[8] These discussions have focused on clinical trial designs for CAP and other important issues such as the following:

- Noninferiority versus superiority design
- Justification of an appropriate noninferiority margin
- Classification of severity of illness
- Classification of CAP based on hospitalization (inpatient versus outpatient)
- Enrollment criteria
- Application of appropriate diagnostic criteria, including microbiologic diagnosis
- Use of appropriate definitions of clinical outcomes
- Timing of outcome assessments
- Use of prior antibacterial drugs

Important changes from the 1998 draft guidance that are based on these discussions have been incorporated into the appropriate sections below.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Definition of CABP

The FDA's previous clinical definition of CAP in an immunocompetent adult patient was an acute infection of the pulmonary parenchyma associated with at least some symptoms of acute infection and accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds and/or localized rales). The patient should not have been hospitalized or resided in a long-term care facility for 14 or more days before the onset of symptoms.

To better identify individuals most likely to have bacterial pneumonia and hence benefit from antimicrobial therapy, this guidance defines CABP in an adult patient as an acute infection of the pulmonary parenchyma associated with symptoms such as fever or hypothermia, chills, rigors, cough, chest pain, or dyspnea, accompanied by the presence of a new lobar or multilobar infiltrate on a chest radiograph.

[8] See http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiInfective.

2. Drug Development Population

The intended trial population should be patients 18 years of age and older with CABP. In addition to the clinical syndrome of bacterial pneumonia previously described, bacteriological confirmation of the etiologic agent (discussed later in this guidance) should be provided in at least 30 to 40 percent of enrolled patients.

3. Pharmacokinetic and Pharmacodynamic Considerations

New antibacterial drugs being studied for CABP should have nonclinical data documenting activity against the most commonly implicated pathogens for CABP (i.e., *S. pneumoniae*, *H. influenzae*, *S. aureus*, and *Moraxella catarrhalis*).

Evaluation of the pharmacokinetic and pharmacodynamic characteristics of an antibacterial drug being developed for CABP can provide useful data to inform dose selection and dosing regimens that should be evaluated in subsequent clinical trials.

Investigation of the pharmacokinetic/pharmacodynamic (PK/PD) characteristics of an antibacterial drug can begin in nonclinical studies. Dose fractionation studies, often conducted in a thigh infection model, can be useful in determining the PK/PD index best associated with activity for a new antibacterial drug. There are also other models such as in vitro hollow-fiber models and in vivo animal infection models (other than the thigh infection model) that can be used to identify or explore the PK/PD index best associated with antibacterial effect as well as the magnitude of the PK/PD index necessary to achieve the desired endpoint. Ideally, animal models of infection exploring antibacterial drug activity should be conducted in neutropenic and immunocompetent mice to evaluate antibacterial drug effect in the setting of either a compromised or intact immune system. Information regarding the pharmacokinetics and lung distribution of the test drug in the species being studied is important in interpreting pharmacodynamic data derived from the animal model.

In addition to thigh infection models, animal models of acute pneumonia have been developed in both mice and rats, particularly for *S. pneumoniae* infection for evaluation of antibacterial therapy.[9,10] The majority of pneumonia models initiate infection by direct instillation into nares and/or trachea, but lung infection also has been initiated using an aerosolization procedure.[11] Reproducible invasive lung infections are more difficult to induce with organisms such as *H. influenzae*.[12] Differences in the effect of animal lung secretions versus human lung secretions on

[9] Tessier, PR et al., 2002, Pharmacodynamic Assessment of Clarithromycin in a Murine Model of Pneumococcal Pneumonia, Antimicrob Agents Chemother, 46:1425-1434.

[10] Gavalda, J et al., 1997, Treatment of Experimental Pneumonia due to Penicillin-Resistant *Streptococcus pneumoniae* in Immunocompetent Rats, Antimicrob Agents Chemother, 41:795-801.

[11] Legget, J, 1999, Murine Models of Pneumonia Using Aerosol Infection, In: Zak O, Sande MA, eds., Handbook of Animal Infections: San Diego, Academic Press, 533-538.

[12] Miyazaki, S et al., 1997, New Murine Model of Bronchopneumonia due to Cell-Bound *Haemophilus influenzae*, J Infect Dis, 175:205-209.

149 the activity of the antibacterial should be evaluated.[13] Although animal models may contribute
150 to providing early proof of concept in the treatment of CABP (or for comparing in vivo activity
151 of different antimicrobials), the results should be carefully interpreted when used to help design
152 subsequent human trials. Animal models also can be used to explore antimicrobial activity
153 against resistant bacteria or specific bacterial serotypes that occur less commonly in clinical
154 trials.[14] Animal studies cannot, however, substitute for the clinical trials in patients with CABP
155 that must be conducted to evaluate drug safety and efficacy because clinical studies can be
156 conducted in patients with CABP.[15]
157
158 The results of PK/PD assessments in animals should be integrated with the findings from phase 1
159 pharmacokinetic studies to help identify the appropriate dosing regimens for evaluation in phase
160 2 and phase 3 clinical trials. A dose-response trial design should be considered as it allows
161 weighing the benefits and risks of various doses and can ensure that excessive doses (beyond
162 those that add to efficacy) are not used, offering some protection against unexpected and
163 unrecognized dose-related toxicity.[16]
164
165 Consideration should be given to obtaining blood samples from all patients in phase 2 and phase
166 3 clinical trials (*sparse sampling*) to allow for the estimation of drug exposure in each patient. A
167 retrospective exposure-response analysis based on the population pharmacokinetic model should
168 be performed to assess the relationship between exposure and observed clinical and
169 microbiologic outcomes. The relationship between drug exposure and clinically relevant adverse
170 events also should be explored to identify potential risks with different dosing regimens (if
171 applicable) and specific patient populations.
172
173 *4. Dose Selection*
174
175 To choose the dose or doses to be evaluated in phase 3 clinical trials, sponsors should integrate
176 the findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics,
177 safety and tolerability information from phase 1 clinical trials, and safety and efficacy
178 information from phase 2 dose-ranging clinical trials. Studies assessing drug penetration at the
179 site of action (e.g., epithelial lining fluid) may be helpful in defining doses that achieve
180 concentrations sufficient to exert an antibacterial effect. In addition, the pharmacokinetics of the
181 drug in specific populations (e.g., geriatric patients, patients with renal or hepatic impairment)
182 should be evaluated before initiation of phase 3 trials to determine whether dose adjustments are
183 necessary. This evaluation may prevent the exclusion of such patients from phase 3 clinical
184 trials.

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[13] Silverman, JA, LI Mortin, AD Vanpraagh, T Li, and J Alder, 2005, Inhibition of Daptomycin By Pulmonary Surfactant: In Vitro Modeling and Clinical Impact, J Infect Dis, 191:2149-2152.

[14] Bender, JM, K Ampofo, K Korgenski et al., 2008, Pneumococcal Necrotizing Pneumonia in Utah: Does Serotype Matter?, Clin Infect Dis, 46:1346-1352.

[15] 21 CFR 314.600 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=314.600)

[16] See the guidance for industry *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications* and the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration* (http://www.fda.gov/cder/guidance/index.htm).

5. Efficacy Considerations

Either noninferiority or superiority trial designs can be used for this indication, but we do not believe that placebo-controlled trials can be ethically conducted for this indication, because placebo-treated patients would be exposed to serious risks.[17] The goal of CABP clinical trials should be to demonstrate an effect of antibacterial therapy on the clinical course of CABP caused by bacterial pathogens such as *S. pneumoniae*, *H. influenzae*, *S. aureus*, or *M. catarrhalis*. If sponsors wish to include additional organisms in clinical trials for this indication, they should provide data sufficient to substantiate the clinical relevance of the particular organism as a pathogen in CABP. Patients with risk factors for infection with drug-resistant organisms such as methicillin-resistant *S. aureus* can be enrolled if the spectrum of activity of both the investigational drug and comparator includes the specific organism.

The number of clinical trials needed to support a CABP indication depends on the overall development plan for the drug under consideration. If the development plan for the drug has CABP as the sole indication, then it would be expected that two adequate and well-controlled trials would support effectiveness. If a drug is being developed for other respiratory infections, sponsors should discuss with the FDA whether other trials might lend support to a CABP indication. A trial in which most patients have documented bacterial pathogens (e.g., *S. pneumoniae*, *H. influenzae*, *S. aureus*, or *M. catarrhalis*) generally will provide the strongest evidence of efficacy. Although a documented bacterial etiology is important for all trial designs, it is particularly critical for noninferiority trials, because the noninferiority margin is based on the evidence from patients with microbiologically documented infections, primarily *S. pneumoniae*. Microbiological confirmation also permits analysis of treatment response by individual pathogen.

For drugs that have only an IV formulation available, we recommend that sponsors conduct trials with the IV formulation alone, without switching to an oral antibacterial drug, to allow for proper assessment of both the efficacy and safety of the test drug. If two adequate and well-controlled trials are being conducted for the indication of CABP, it may be appropriate to allow oral switch in one of the trials, provided adequate safety data are available from other indications. If this approach is taken, the IV antibacterial should be administered for a minimum length of time (e.g., 72 to 96 hours) before switching to oral therapy. Objective criteria that allow for oral switch should be specified in the protocol and captured on the case report form. Clinical assessment should be performed at the time of IV to oral switch.

For drugs that have both an IV and oral formulation, appropriate criteria that allow for IV to oral switch should be specified in the protocol. The pharmacokinetics of the oral formulation should have been adequately evaluated to ensure comparable exposure and to determine an appropriate dosing regimen. These criteria should be listed on the case report form. If practice patterns allow, it may be appropriate to enroll hospitalized CABP patients in oral antibacterial trials.

[17] See the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (http://www.fda.gov/cder/guidance/index.htm).

Currently, we do not recognize any surrogate markers as a substitute for clinical outcomes in CABP trials. Sponsors who wish to propose a surrogate marker for clinical outcome or the initial diagnosis of CABP 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, 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 CABP. 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. Trial Design

CABP trials should be randomized, double-blind, and active-controlled using a noninferiority or superiority design. Placebo-controlled trials are not appropriate for this indication.

2. Trial Population

The trial population should include patients 18 years of age and older with CABP. The trials should enroll patients with either confirmed CABP or with a high likelihood of CABP. An adequate number of patients with bacteriologically confirmed infections should be enrolled to allow assessment of the drug's effectiveness based upon the prespecified noninferiority margin, as described in section III.B.12., Statistical Considerations.

3. Inclusion and Exclusion Criteria

a. Clinical, radiographic, and microbiologic criteria

The diagnosis of CABP should be based on the following clinical, radiographic, and microbiologic criteria.

- **Clinical criteria.**
  - As part of the clinical picture of CABP, a patient should have at least three of the following symptoms and signs:
    - Cough with production of purulent sputum
    - Dyspnea or tachypnea
    - Chest pain
    - Fever, defined as body temperature greater than 38 degrees Celsius (100.4 degrees Fahrenheit) taken orally, greater than 38.5 degrees Celsius (101.2 degrees Fahrenheit) tympanically, or greater than 39 degrees Celsius (102.2 degrees Fahrenheit) rectally; or hypothermia (less than 35 degrees Celsius)[18]
    - Clinical findings of pulmonary consolidation (e.g., dullness on percussion, bronchial breath sounds, or egophony)
  - Additional criteria that may support the diagnosis of CABP but not needed for inclusion are as follows:
    - Chills or rigors
    - Hypoxemia with a $PO_2 < 60$mm Hg while patient is breathing room air
    - An elevated total white blood cell count or leukopenia, or elevated immature neutrophils (bands)
  - We recommend using the Pneumonia Severity Index or Pneumonia Patient Outcomes Research Team (PORT) classification system for the purposes of enrollment and stratification.[19] The criteria that are used to calculate the PORT score and determine the risk class for each patient should be included in the case report form and in the datasets.
    - *IV antibacterials.* All patients being enrolled in IV antibacterial trials should have PORT scores of II or greater. No more than 25 percent of the enrolled population should have a PORT score of II and at least 25 percent of the population should have PORT scores of IV or greater.

[18] Some patients develop hypothermia, especially the elderly and others who have risk factors such as alcoholism, malnutrition, and other comorbid illnesses.

[19] Fine, MJ, TE Auble, DM Yealy et al., 1997, A Prediction Rule to Identify Low-Risk Patients with Community-Acquired Pneumonia, N Engl J Med, 336:243-50.

312 ▪ *Oral antibacterials.* Patients being enrolled in oral antibacterial trials should have
313 PORT scores of II or greater. At enrollment, at least 50 percent of these patients
314 should have PORT scores of III or greater.
315
316 • **Radiographic criteria.** The chest radiograph should show the presence of new
317 infiltrates in a lobar or multilobar distribution characteristic of bacterial pneumonia. The
318 final full report of the pretreatment and subsequent chest radiograph by the radiologist
319 should be included in the case report form.
320
321 • **Microbiologic criteria.** At the time of enrollment, an adequate specimen of respiratory
322 secretions should be obtained in all patients and sent to the laboratory for Gram stain,
323 culture, and in vitro antibacterial susceptibility testing performed on appropriate
324 organisms isolated from the specimen. Specimens should be processed according to
325 recognized methods.[20] Microscopic examination of Gram stained smears should be
326 performed. Specimens that have fewer than 10 squamous epithelial cells and more than
327 25 polymorphonuclear cells per low power field (100X magnification) are considered
328 appropriate for inclusion in evaluation of respiratory culture results. Ten to twenty fields
329 of the Gram stain smear also should be examined at 1000X magnification and the
330 morphology of potential pathogens recorded. The Gram stain should be performed and
331 the specimen plated for culture within 2 hours from the collection time, if the specimen is
332 kept at room temperature. Alternatively, these tests can be performed within 24 hours of
333 collection if the specimen is stored at 2 to 8 degrees Celsius before processing.
334
335 The specimen of respiratory secretions can be obtained by any of the following means:
336
337 – Deep expectoration
338 – Endotracheal aspiration in intubated patients
339 – Bronchoscopy with bronchoalveolar lavage or protected-brush sampling
340
341 All isolates considered to be possible pathogens should be saved in the event that
342 additional testing of an isolate is needed. For microbiological assessment, the
343 investigator should collect the following information:
344
345 – A description of how the sample was obtained, processed, and transported to the
346 laboratory.
347
348 – Identification of the bacterial isolate and serotype if *S. pneumoniae*.
349
350 – In vitro susceptibility testing of the isolates to both the study drug and other
351 antibacterials that may be used to treat CABP caused by the targeted pathogens. In
352 vitro susceptibility should be performed by using standardized methods unless

[20] American Society for Microbiology, 2007, Manual of Clinical Microbiology, 9th edition.

otherwise justified.[21] 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 (e.g., urinary antigen test for *S. pneumoniae*) or for respiratory viral pathogens; 2) microbiologic testing for bacterial pathogens associated with atypical pneumonia such as *L. pneumophila*, *M. pneumoniae*, or *C. pneumoniae*; and 3) use of biomarkers for detection of bacterial pathogens.

b. Exclusion criteria

Exclusion criteria include the following:

- Atypical pneumonia
- Viral pneumonia
- Aspiration pneumonia
- Hospital-acquired pneumonia, including ventilator-associated pneumonia
- Receipt of prior antibacterials (see section III.B.7., Prior Antibacterial Drug Use)
- Patients with known bronchial obstruction or a history of post-obstructive pneumonia (this does not exclude patients who have chronic obstructive pulmonary disease)
- Patients with primary or metastatic lung cancer
- Patients with cystic fibrosis, known or suspected *Pneumocystis jiroveci* pneumonia, or known or suspected active tuberculosis

4. Randomization, Stratification, and Blinding

Patients should be randomized to treatment groups at enrollment. All trials should be double-blind unless there is a compelling reason for unblinding.

We recommend stratification by age (e.g., younger than 50 years, 50 years of age or older) and PORT scores (as outlined for entry criteria in section III.B.3.a., Clinical, radiographic, and microbiologic criteria).

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

5. Special Populations

The trials should include patients 18 years of age and older, of both sexes, and all races. If sponsors wish to pursue CABP trials in pediatric patients, they should discuss the development plans with the FDA. Patients with renal or hepatic impairment can be enrolled provided pharmacokinetics of the drug have been evaluated in these patients and appropriate dosing regimens have been defined.

6. Choice of Comparators

Placebo-controlled trials are not appropriate for this indication. The active comparator should be an FDA-approved antibacterial that is considered standard of care for this indication (e.g., guidelines published by professional societies) at the recommended dosage.

7. Prior Antibacterial Drug Use

The use of prior antibacterial drugs effective against bacteria that cause CABP should be avoided in a noninferiority trial (except as described below) because such treatments will reduce the difference between treatment arms and allow an incorrect conclusion of noninferiority. However, patients who have received prior antibacterial therapy and who are considered clinical failures can be enrolled provided objective criteria for treatment failure are prespecified and documented on the case report form. Also, patients can be enrolled if they have received prior antibacterial therapy that lacks in vitro activity against the baseline pathogen.

8. Concomitant Medications

Concomitant antibacterial therapy for other infections should not be allowed during the trial until after the test-of-cure visit. Patients who receive such therapy should be excluded from the evaluable population and will be considered failures in the intent-to-treat (ITT) and the modified intent-to-treat (MITT) populations. Patients requiring rescue antibacterial therapy should be considered treatment failures and should be included in the ITT, MITT, and per-protocol populations.

9. Efficacy Endpoints

a. Primary endpoints

The following primary endpoints can be considered for CABP trials.

- **Primary clinical outcome based on complete resolution of signs and symptoms measured at a fixed time point**
  - *Clinical success.* A patient who is alive and has resolution of disease-specific signs and symptoms present at enrollment and who has no new symptoms or complications attributable to CABP is defined as a clinical success.[22]

[22] Some patients may have a prolonged cough despite resolution of other signs and symptoms of CABP. Such patients can be considered clinical successes provided they are not given additional antibacterials and are followed until resolution of the cough.

- *Clinical failure.* Patients designated as clinical failures at an early time point should be designated as clinical failures for all subsequent follow-up visits. Clinical failure is defined as follows:
  - All-cause mortality within 30 days of start of study drug
  - Lack of resolution of baseline CABP-specific signs and symptoms at the test-of-cure visit
  - Progression or development of new symptoms or radiologic findings attributable to CABP at any time point after enrollment
  - Development of complications of CABP such as empyema or lung abscess
  - Need for rescue therapy with nonstudy antibacterial drugs

- **Primary clinical outcome based on time to resolution of signs and symptoms**

  Currently, endpoints based on time to resolution of signs and symptoms are only applicable to superiority trials because an appropriate noninferiority margin has not been defined. If a patient-reported outcome (PRO) tool is used, its content validity and other measurement properties should be demonstrated in the population represented in the clinical trial. Relevant details regarding the planned trial design, analysis, and interpretation of the PRO findings should be discussed with the FDA before trial initiation.

b. Secondary endpoints

Sponsors can present secondary analyses on endpoints such as time to resolution of signs and symptoms (where the primary endpoint is complete resolution) or other endpoints of interest.

Sponsors should be aware that analyses of secondary and additional endpoints usually will be considered 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 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.

c. Patient-reported outcome instruments

A PRO instrument can be used to measure patient symptoms and self-reported signs. If a PRO instrument is used for measuring responses that will be based on a scaled score, then the score rather than an endpoint of complete symptom resolution should be used as the outcome variable. An outcome scale can be used for describing categorical responses (e.g., *success*, *improvement*, and *failure*) at each time point if the criteria for the categories have been well-developed and

validated. If an alternative to a PRO is used, the method of assessment should be a well-defined and reliable method of assessing patient response. Any tool used to assess time to resolution of signs and symptoms should be discussed with the FDA before trial initiation.

Because no PRO instrument has been recognized by the FDA for this indication, exploratory testing of a well-developed PRO instrument in clinical trials may justify its use to support primary or secondary study objectives in subsequent trials. Development of the new instrument should begin well in advance of phase 3 clinical trials so that the instrument can be ready for incorporation into the phase 3 protocol. If the PRO tool is not developed for assessment of the primary endpoint, it may be appropriate to evaluate its use for assessment of secondary endpoints.

For more information regarding the development of such outcome measures, see the draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.[23]

10. Trial Visits 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
- Baseline signs and symptoms including vital signs
- Chest X ray
- PORT score criteria and calculation
- Microbiologic specimens: adequate sputum specimens as determined by Gram stain (see section III.B.3.a., Clinical, radiographic, and microbiologic criteria), sputum culture, blood cultures, other rapid diagnostic tests
- Laboratory tests: hematology, chemistry, and others as appropriate

b. On-therapy visits

Each patient should have on-therapy assessments of signs and symptoms. The frequency of these visits depends on whether the endpoint is assessed at a fixed time point or a time-to-resolution endpoint is used. The ability to detect differences between study therapies for a time-to-resolution endpoint may be increased if assessments are done more often. These assessments

[23] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

can be performed by the investigator during a visit to the investigator's office or by a validated PRO instrument. Patients should be clinically evaluated by the investigator at a 48- to 72-hour visit to ensure that there is no clinical worsening at this time.

Assigning clinical failure and permitting use of rescue antibacterial therapy should be reserved for patients who are worsening or not improving on their assigned treatment arm; specific criteria to initiate rescue therapy in these patients should be included in the protocol. Appropriate specimens for microbiologic evaluation should be obtained in these patients before instituting the new antibacterial therapy. 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. In the case of clinical failure, therapy should be changed to an appropriate alternative antibacterial treatment for CABP, with other therapeutic modifications as necessary. Patients who receive rescue therapy should continue to have protocol-specified assessments identical to patients who continue to receive their originally assigned treatment and will be considered treatment failures in both complete resolution and time to resolution endpoints.

Investigators should document findings from on-therapy office visits (e.g., history, physical examination, and laboratory test results) on the patient case report form. If the investigator contacts the patient by telephone or by another interactive technology, documentation of the specific questions asked, how they were asked, and the responses given should be captured on the case report form. If a validated diary is used to capture patient symptoms during this trial, this information should also be recorded on the patient case report form.

c. 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 study 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 failures and alternative antibacterial rescue therapy should be provided.

d. Test-of-cure visit

The test-of-cure visit should occur after completion of study drug at a time when the drug is expected to have cleared from the infection site. The test-of-cure visit should occur at a fixed time point relative to randomization (5 to 10 days after completing therapy). If the treatment durations in the test and control arms are different, the timing should be based on the longest treatment duration. For drugs with long half-lives, sponsors should discuss the timing of the visits with the FDA during protocol development. At this visit, the investigator should obtain medical history including adverse events, perform physical examination, and obtain appropriate laboratory and radiological measurements.

e. Follow-up assessment

The follow-up assessment should occur approximately 1 to 2 weeks after the test-of-cure visit. This assessment can be performed by a telephone contact with patients who were considered to be clinical successes and had no adverse events noted at the test-of-cure visit. For patients with adverse events occurring at or after the test-of-cure visit, investigators should perform an assessment that includes a medical history, a physical examination, appropriate laboratory evaluations, and identification of any new adverse events. All adverse events should be followed to resolution. It is important that all patients are followed for at least 30 days after enrollment to capture the 30-day mortality data.

11. Endpoint Adjudication

Generally in CABP trials, there is no need for endpoint adjudication. If a sponsor believes that adjudication or endpoint assessment committee is necessary, this should be discussed with the FDA before trial initiation.

12. Statistical Considerations

The trial hypotheses and the analysis methods should be stated in the protocol and/or the statistical analysis plan, and should be finalized before trial initiation. Changes in statistical analysis plans made later may be appropriate if made entirely blindly; however, documenting unequivocal maintenance of the blind can prove difficult. The trials should be adequately powered to detect differences between treatment arms if differences exist. If sponsors choose to test multiple hypotheses, they should address issues related to the potential inflation of false positive results (overall type I error rate) because of multiple comparisons. 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.[24]

a. Analysis populations

The following definitions apply to various analysis populations in CABP clinical trials:

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

- ITT population — All patients who were randomized.

- MITT population (also sometimes referred to as microbiological intent-to-treat population) — All randomized patients who have a baseline bacterial pathogen known to cause CABP against which the test drug has antibacterial activity. This includes bacterial pathogens identified in blood, appropriate sputum specimen, or other test such as urinary antigen test. Patients should not be excluded from this population based upon events that occur postrandomization (e.g., loss to follow-up).

[24] See ICH E9 and ICH E10 (http://www.fda.gov/cder/guidance/index.htm).

- 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.

Generally, ITT analyses are preferred for superiority trials, although use of the MITT population may greatly increase the chance of demonstrating effectiveness by excluding patients who do not have the disease under study. Although the ITT population is usually the primary analysis in a difference-showing trial, the inherent bias toward the null in noninferiority trials poses a significant problem, and in this case ITT may not be the preferred analysis.[25] Particularly where the noninferiority margin is based primarily on microbiologically defined patients, the MITT population is preferred. Moreover, for similar reasons, the microbiologically evaluable population should be strongly considered. In addition, consistency of results should be evaluated in the ITT and clinically evaluable populations.

b. Noninferiority margins

Based on a review of the historical data, we believe that noninferiority trials are appropriate for the CABP indication (see Appendix). This issue was discussed at the Anti-Infective Drugs Advisory Committee meeting in April 2008. The noninferiority margins can be justified based on historical evidence of the treatment effect of antibacterial therapy on mortality in patients with lobar or pneumococcal pneumonia. Sponsors should justify the noninferiority margin for the proposed trial design and population enrolled. In the final trial report, sponsors should address issues relating to the noninferiority margin as it applies to the trial population.

For drugs with an IV formulation, the MITT population will be considered as the primary analysis population and a 15 percent noninferiority margin is appropriate. However, as outlined in section III.B.3., Inclusion and Exclusion Criteria, no more than 25 percent of patients enrolled should have PORT scores of II and a minimum of 25 percent of patients should have a PORT score of IV or greater.

For drugs with only an oral formulation, the MITT population will be considered as the primary analysis population and a 10 percent noninferiority margin is appropriate. As outlined in section III.B.3., Inclusion and Exclusion Criteria, patients with a PORT score of I should be excluded and at least 50 percent of the population should have a PORT score of III or greater.

c. Sample size

The appropriate sample size for a clinical trial should be based upon the number of patients needed to answer the research question posed by the trial. The sample size is influenced by several factors including the prespecified type I and type II error rates, the expected success rate,

[25] See ICH E10 (http://www.fda.gov/cder/guidance/index.htm).

the noninferiority margin (for a noninferiority trial), or the amount by which the study 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 single 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. Sponsors also should present sensitivity analyses such as including all missing patients as failures or including all missing patients as successes. Interpretation of trial results may be affected if the rates of missing data are different across treatment arms.

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 (if any). It is important that the interim analysis not affect trial conduct and thereby compromise trial results. This can be accomplished by creating an independent data monitoring committee (DMC). 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, decision rules, details on the measures taken to protect the integrity of the trial, and the standard operating procedures should be provided for review.[26]

f. Other analyses of interest and secondary endpoints

Sponsors can present secondary analyses on other endpoints of interest such as:

- Mortality and clinical response in bacteremic versus nonbacteremic patients
- Response at earlier time points or at the end of therapy
- Response based on patient demographics such as age, geographic region, underlying renal impairment, and microbiologic etiology

g. Statistical analysis plan

Before initiation of any phase 3 CABP trial, sponsors should provide a detailed statistical analysis plan to the FDA.

[26] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (http://www.fda.gov/cder/guidance/index.htm).

13. Risk-Benefit Considerations

Risk-benefit considerations depend on the population being studied and the safety profile of the drug being investigated.

C. Other Considerations

1. Labeling Considerations

The labeled indication will be community-acquired bacterial pneumonia caused by the specific bacteria identified in patients in the clinical trials and will reflect the patient population enrolled in the clinical trials.

2. Antimicrobial Resistance Claims

To obtain a claim for resistant pathogens in CABP, the claim should be relevant to CABP and sponsors should present data from their clinical trials to demonstrate treatment effect with the drug against resistant organisms. Sponsors seeking resistance claims for CABP are encouraged to contact the review division regarding appropriate trial designs for resistant pathogens and to discuss the desired resistance claims.

APPENDIX: NONINFERIORITY MARGIN JUSTIFICATION FOR CABP

Background

Conceptually, the selection of a noninferiority margin is a two-step process. The first step involves reliable estimation of the treatment effect of the active comparator (i.e., effect of the active comparator over placebo, referred to as M1) based upon placebo-controlled trials. When data from placebo-controlled trials are not available, an alternative means to estimate treatment effect is to use available data from trials of treated versus untreated disease, remaining conscious of the risks of cross-study comparisons. All use of such historical estimates of treatment effect relies on the *constancy* assumption, the assumption that the past effect of the active control is the effect it will have in the contemporary noninferiority trial. For example, if the present effect is in doubt because of changes in ancillary therapy, it may be necessary to *discount* the historically based estimate of the control effect. The estimate of M1 includes any such discounting. The second step involves clinical judgment regarding how much of the estimated treatment effect (M1) should be preserved in determining a clinically acceptable noninferiority margin, referred to as M2.

Because no data from placebo-controlled trials in CAP are available, we reviewed results from historical comparative clinical trials of treated versus untreated controls and from observational studies that evaluated mortality in patients treated with antibacterial drugs or with no specific therapy to estimate the treatment effect of antibacterial drugs in CAP. Based on review of these data, we believe that noninferiority trials are appropriate for the specific indication of CABP, as described in this guidance. Historical studies and clinical trials of antibacterial treatment of pneumonia provide evidence that antibacterial drugs reduced mortality in patients with pneumococcal or lobar pneumonia. Although the treatment effect varied across studies and clinical trials, the effect of treatment on survival was consistently greater in older patients (older than 50 years) and in patients with bacteremia.

Direct extrapolation of treatment effect from historical studies and clinical trials to contemporary CABP clinical trials is difficult. The historical-controlled clinical trials lacked blinding and randomization as currently defined. There is also considerable uncertainty regarding the similarity of patient populations from historical studies and clinical trials to populations in current clinical trials. For example, patients today may have different comorbidities and risk factors for pneumonia, or may have received pneumococcal vaccine. Additionally, improved standards of medical care today may result in improved outcomes (e.g., care in an intensive care unit, mechanical ventilation, hemodynamic support).

Another area of uncertainty in extrapolating the treatment effect of antibacterial drugs from historical studies and clinical trials is the spectrum of bacterial pathogens that cause CABP today in comparison to the early mid-twentieth century. In most of the historical studies and historical-controlled clinical trials, CAP was considered synonymous with pneumococcal pneumonia, whereas in recent CAP clinical trials, less than 20 percent of patients enrolled had documented *S. pneumoniae*.[27] Although *S. pneumoniae* remains the most common cause of CAP, we know that

[27] Higgins, K, M Singer, T Valappil, S Nambiar, D Lin, and E Cox, 2008, Overview of Recent Studies of Community-Acquired Pneumonia, Clin Infect Dis, 47 (Suppl 3) S150-S156.

CAP also can be caused by other pathogens such as *H. influenzae* or *parainfluenzae*, *S. aureus*, and *M. catarrhalis*; atypical bacteria such as *M. pneumoniae* and *C. pneumoniae*; and *Legionella* species, as well as respiratory viruses. Limited information is available on antibacterial treatment effect in CAP caused by *M. pneumoniae*, whereas for pathogens such as *C. pneumoniae*, the size of the treatment effect remains unknown.

Most of the historical studies and clinical trials reported mortality as the clinical outcome. Mortality has not been used as a primary endpoint in recent CAP clinical trials, although it has been a part of the composite endpoint of clinical failure. For noninferiority trials, extrapolating quantitative estimates of treatment benefit from a mortality endpoint to a clinical failure endpoint raises questions regarding the applicability of the treatment effect for mortality to other outcome measures. In current clinical trials, patients who are not improving on therapy would be considered clinical failures, and alternative antibacterial treatment (i.e., rescue therapy) would be initiated before death occurs. The endpoint of clinical failure in a present-day clinical trial includes patients who would have progressed to death in a historical study or clinical trial, but it may include others who ultimately would not have died. Thus, it appears reasonable to include in current trials death, disease progression, and lack of clinical improvement as an appropriate endpoint that reasonably well reflects past effects on mortality.

Although some of the historical studies and clinical trials attempted to grade severity of illness, descriptions of how severity was assessed were limited. The PORT score, which classifies patients by prognosis (risk of mortality) based on age and other criteria, is used for clinical decision making regarding hospitalization. Current treatment guidelines recommend hospitalization of patients who have a PORT score of III or greater.[28] The PORT score is weighted heavily by age, and the majority of patients with PORT scores of III or greater will be over 50, have significant comorbidities, or have severe physiologic derangements upon presentation.

Historical studies and trials

Observational

In several observational studies of pneumococcal pneumonia, a significant mortality benefit was shown among patients treated with antibacterial drugs compared to patients who received no specific therapy (untreated), as summarized in Table A1.

[28] Fine, MJ, TE Auble, DM Yealy, BH Hanusa, LA Weissfeld, DE Singer, CM Coley, TJ Marrie, and WN Kapoor, 1997, A Prediction Rule to Identify Low-Risk Patients with Community-Acquired Pneumonia, N Engl J Med, 336:243-50.

Table A1. Mortality in Observational Studies of Pneumococcal Pneumonia[1]

Publication	Population	Mortality (%) Untreated N (Study Years)	Mortality (%) Antibacterial-Treated	Treatment Difference Untreated-Treated (95% Confidence Interval)
Finland (1943)[2]	≥ 12 years old bacteremic and nonbacteremic	N=2,832 (1929-1940)* 41%	N=1,220 (1939-1941) 17% (sulfonamides)	24% (21,27)
Dowling and Lepper (1951)[3]	≥ 10 years old bacteremic and nonbacteremic	N=1,087 (1939, 1940)* 30.5%	N=1,274 (1938-1950) 12.3% (sulfonamides) N=920 (1938-1950) 5.1% (penicillins and tetracyclines)	18.5% (15,21) 25.4% (22,28)
Austrian and Gold (1964)[4]	≥ 12 years old bacteremic	N=17 (1952-1962) 82%	N=437 (1952-1962) 17%	65% (41,79)

[1] Singer, M, S Nambiar, T Valappil, K Higgins, and S Gitterman, 2008, Historical and Regulatory Perspectives on the Treatment Effect of Antibacterial Drugs for Community-Acquired Pneumonia, Clin Infect Dis, 47 (Suppl 3): S216-S224.
[2] Finland, M, 1943, Chemotherapy in the Bacteremia, Conn State Med J, 7:92-100.
[3] Dowling, HG and MH Lepper, 1951, The Effect of Antibiotics (Penicillin, Aureomycin and Terramycin) on the Fatality Rate and Incidence of Complications in Pneumococcic Pneumonia: A Comparison with other Methods of Therapy, AM J Med Sci, 222:396-402.
[4] Austrian, R and J Gold, 1964, Pneumococcal Bacteremia with Especial Reference to Bacteremic Pneumococcal Pneumonia, Ann Intern Med, 60:759-776.
* Historical controls

Despite the many limitations of these historical studies, such as observational study design and use of historical controls, the mortality benefit demonstrated with antibacterials was substantial. The lower limit of the 95 percent confidence interval (CI) for the treatment difference (antibacterials minus placebo) from the Finland study was 21 percent. In the Dowling and Lepper study, the lower limit of the 95 percent CI for the treatment difference (antibacterials minus placebo) was 15 and 22 percent for patients who received sulfonamides or penicillins and tetracyclines respectively; the latter group seems more likely to reflect the effect of modern antibacterial treatments. In the Austrian and Gold study, which only evaluated patients with bacteremic pneumococcal pneumonia, the lower limit of the 95 percent CI was 41 percent. In these studies of pneumococcal pneumonia, the mortality difference between antibacterial-treated and untreated groups was largest in patients older than 50 years, in patients treated with penicillin or tetracyclines rather than sulfonamides, and in patients with pneumococcal bacteremia.

The mortality associated with pneumonia is greatest at the extremes of age. Persons over the age of 50 years exhibit the greatest mortality, and correspondingly antibacterial therapy has its

greatest effect in reducing mortality in these populations. This observation is apparent from looking at the data from Dowling and Lepper in patients with pneumococcal pneumonia, as shown in Table A2.

Table A2. Mortality By Age from Dowling and Lepper (1951)[1]

Age (Years)	Untreated		Sulfa-Treated		Penicillin, Tetracycline-Treated		Serum-Treated	
	N	Deaths (%)	N	Deaths (%)	N	Deaths (%)	N	Deaths (%)
10 to 49	725	139 (19.2)	988	79 (8.0)	684	18 (2.6)	710	74 (10.4)
50 to > 70	362	192 (53.0)	286	78 (27.3)	236	20 (12.3)	179	76 (42.5)
Total	1,087	331 (30.5)	1,274	157 (12.3)	920	47 (5.1)	889	150 (16.9)

[1] Dowling, HG and MH Lepper, 1951, The Effect of Antibiotics (Penicillin, Aureomycin and Terramycin) on the Fatality Rate and Incidence of Complications in Pneumococcic Pneumonia: A Comparison with other Methods of Therapy, AM J Med Sci, 222:396-402.

As shown in Table A3, an approximate doubling of the size of the treatment effect with antibacterial drugs is noted in patients older than 50 years compared to patients younger than 50 years.

Table A3. Treatment Difference By Age in Patients with Pneumococcal Pneumonia from Dowling and Lepper (1951)[1]

Treatment	Age	Treatment Difference (% Death Untreated- % Death Treated)
Sulfa	< 50	11.2 (7.8, 14.5)
	≥ 50	25.8 (18.5, 33.1)
Penicillin, tetracycline	< 50	16.5 (13.4, 19.6)
	≥ 50	44.6 (38.3, 50.8)
Serum	< 50	8.7 (5.1, 12.4)
	≥ 50	10.6 (1.7, 19.5)

[1] Dowling, HG and MH Lepper, 1951, The Effect of Antibiotics (Penicillin, Aureomycin and Terramycin) on the Fatality Rate and Incidence of Complications in Pneumococcic Pneumonia: A Comparison with other Methods of Therapy, AM J Med Sci, 222:396-402.

Controlled trials

In the historical-controlled clinical trials in patients with lobar pneumonia, the point estimates for the treatment difference for mortality in patients treated with sulfapyridine or no specific therapy varied from 10 to 19 percent for all ages combined, as shown in Table A4. The CI for each of the trials (or subtrials) are wide, as the number of patients enrolled in most of these trials was small. A high proportion of the population in these trials was younger than 50 years of age, a group in which the treatment effect was smaller in the observational studies. The numbers of patients in these trials was not sufficient to provide informative estimates of the effect of age on mortality.

Table A4. Mortality in Historical-Controlled Trials of Lobar Pneumonia[1]

Publication	Population	Mortality (%) Untreated N	Mortality (%) Antibacterial-Treated	Treatment Difference Untreated-Treated (95% Confidence Interval)
Evans and Gaisford (1938)[2]	8-68 years old, 86% < 50 years old; specific serotypes identified in 22%, bacteriology in remainder not described	27/100 (27%)	8/100 (8%)	19% (8.8, 29.2)
Graham (1938)[3]	86% had pneumococcal pneumonia, 29% bacteremic, 70% < 50 years old	7/30 (23%)	3/50 (6%)	17% (0.1-36.4)
Agranat (Europeans substudy, 1938)[4]	97% < 50 years old, frequency of bacteremia not reported	6/27 (22%)	2/22 (7%)	15% (-6.2, 35.5)
Agranat (Non-Europeans substudy, 1938)[4]	81% < 50 years old, frequency of bacteremia not reported	16/86 (19%)	6/71 (9%)	10% (-0.3, 20.6)

[1] Singer, M, S Nambiar, T Valappil, K Higgins, and S Gitterman, 2008, Historical and Regulatory Perspectives on the Treatment Effect of Antibacterial Drugs for Community-Acquired Pneumonia, Clin Infect Dis, 47 (Suppl 3): S216-S224.

[2] Evans, GM and WF Gaisford, 1938, Treatment of Pneumonia with 2-(aminobenzenesulphonamido) pyridine, Lancet, 2:14-19.

[3] Graham, D, WP Warner, JA Dauphinee, and RC Dickson, 1939, The Treatment of Pneumococcal Pneumonia with Dagenan (M. & B. 693), Can Med Assoc J, 40:325-332.

[4] Agranat, AL, AO Dreosti, and D Ordman, 1939, Treatment of Pneumonia with 2-(aminobenzenesulphonamido) pyridine (M. & B. 693), Lancet, 1:309-317.

Estimation of M1

The estimate of the treatment effect should take into consideration several sources of uncertainty while relying upon the data from previously conducted studies and clinical trials as discussed below:

- The first source of uncertainty is the precision of the estimate of the treatment effect from the historical data. The 95 percent CIs have been used to estimate the range within which the true treatment effect is likely to fall.

- The second source of uncertainty arises from the issue of whether the magnitude of the treatment effect that was observed in previously conducted studies and clinical trials will be different from that which would be seen in a future clinical trial (i.e., constancy assumption).

- The third source of uncertainty is type I error (concluding that the test drug is noninferior when it is not). The issue of type I error in a present-day CABP trial is controlled through choosing an alpha of two-sided 0.05 (i.e., one-sided 0.025) as a means to control for alpha error.

Acknowledging the uncertainties inherent in the historical data, an estimate of the treatment effect from the observational studies, based on the lower bound of the 95 percent CI, is 22 percent for penicillins and tetracycline in patients with pneumococcal pneumonia and 15 percent for sulfa drugs in treating pneumococcal pneumonia. For the three controlled trials, we performed a meta-analysis using a random effects model to control for intratrial variability. The point estimate for the treatment difference and the corresponding 95 percent CI was 15.1 percent (8.8 percent, 21.4 percent). Several factors should be considered in interpreting the lower bound of 8.8 percent derived from this meta-analysis when estimating the treatment effect for a present-day CABP trial with designs as described in this guidance.

This estimate of the treatment effect may be an underestimate for the following reasons:

- The vast majority (at least 70 percent) of patients in the controlled trials were younger than 50 years of age. Based on data from observational studies in pneumococcal pneumonia, it is evident that mortality increases with age and the treatment effect in patients 50 years of age and older is much larger than that seen in patients younger than 50 years of age. The design for present-day CABP trials as described in this guidance will enroll patients with a set distribution of PORT scores and hence enroll an adequate number of patients 50 years of age or older.

- All patients in the controlled trials were treated with oral sulfonamides, which were dosed sub-optimally in some patients in at least two of the trials in Table A2. In the observational studies of pneumococcal pneumonia, the treatment effect based on mortality was greater with penicillins than with sulfonamides (see Table A1). For a present-day CABP trial, the treatment effect is likely to be larger considering that more effective therapies and optimal dosage regimens are used in the clinical trials.

- The treatment effect for an endpoint such as clinical failure would likely be larger than that seen with a mortality endpoint. 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 endpoint 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 endpoint in a present-day trial that includes both mortality and clinical failure. It is important to note that any differential

effect on mortality should be assessed independent of its inclusion in the composite endpoint.

This estimate of the treatment effect may be an overestimate for the following reasons:

- Predominance of data in the historical studies and clinical trials was derived from patients with pneumococcal disease compared to the mixture of microbial etiologies that would likely be present in a present-day CABP trial.

- Advances in supportive care such as mechanical ventilation, blood pressure support, and other intensive care interventions may reduce the mortality observed in a present-day trial compared to what was seen in the 1930s and 1940s.

- The general health status of patients may be somewhat better in a present-day CABP trial. Factors such as improved nutritional status, use of pneumococcal vaccine, underlying comorbidities such as diabetes, or immunocompromise may affect the outcome of pneumococcal disease.

Contemporary CAP clinical trials

In a review of previously conducted clinical trials of oral antibacterial drugs for CAP the median and mean ages were 45 and 46 years of age, respectively.[29] Ninety to ninety-five percent of patients in these CAP trials had PORT scores of I or II and 5 to 10 percent had a PORT score of III. In trials of intravenous drugs for CAP, enrolled patients were somewhat older with a mean age of 56 years; the corresponding PORT scores for these trials were 55 percent PORT I or II, 20 percent PORT III, 20 percent PORT IV, and less than 5 percent PORT V.

Because of the differences in historical studies and clinical trials and present-day CAP trials, we also examined data from a more recent daptomycin trial that provide some insight into the treatment effect of antibacterial drugs in CAP.[30] We present some analyses discussed in the paper and discuss results of additional analyses performed by the FDA.

Two clinical trials were conducted comparing daptomycin to ceftriaxone in the treatment of patients with CAP caused by Gram-positive organisms. The second trial was terminated early based on failure of the first trial to demonstrate noninferiority. Data presented are aggregate data from the two trials. The data provide useful information on the questions of the effect of prior antimicrobial therapy on treatment outcomes and whether these effects vary by PORT score. The mean age was 55 years and the distribution of PORT scores was approximately 42 percent PORT II, 30 percent PORT III, and 28 percent PORT IV.

[29] Higgins, K, M Singer, T Valappil, S Nambiar, D Lin, and E Cox, 2008, Overview of Recent Studies of Community-Acquired Pneumonia, Clin Infect Dis, 47 (Suppl 3) S150-S156.

[30] Pertel, PE, P Bernardo, C Fogarty et al., 2008, Effects of Prior Effective Therapy on the Efficacy of Daptomycin and Ceftriaxone for the Treatment of Community-Acquired Pneumonia, Clin Infect Dis, 46:1142-51.

In these trials, prior antibacterial therapy was defined as any potentially effective antibacterial drug received within 72 hours of starting study drug. Patients were excluded if they had received potentially effective antibacterial therapy for more than 24 hours within 72 hours of enrollment. In the published post-hoc analysis of these trials, prior effective therapy was defined as antibacterial drugs with both greater potency and longer half-lives (such as levofloxacin, ceftriaxone, azithromycin, and clarithromycin). Patients who had received no antibacterial drugs or only drugs with lesser potency or shorter half-lives (such as penicillins, tetracyclines, or trimethoprim-sulfamethoxazole) were classified as having received no prior effective therapy.

As shown in Table A5, in subgroup analyses in the clinically evaluable population of the aggregated daptomycin CAP trials, it appears that prior antibacterial therapy of 24 hours or less duration within the 72-hour period before enrollment has an effect on clinical response and could lessen the treatment effect that an experimental drug could demonstrate. Prior antibacterial therapy had a greater effect on the cure rates in the daptomycin arm compared to the ceftriaxone arm. Similar results were seen in the ITT and MITT populations. Although these are post hoc analyses of subgroups from the aggregate trial data, they suggest the importance of limiting or avoiding prior antibacterial therapy and that prior antibacterial therapy may reduce the treatment effect of an antibacterial drug under study.

Table A5. Effect of Prior Antibacterial Therapy on Clinical Response By Treatment Arm (Clinically Evaluable Populations)[1]

Clinical Response	Prior Antibacterial Therapy		Treatment Difference (95% Confidence Interval)	No Prior Antibacterial Therapy		Treatment Difference (95%Confidence Interval)
	Daptomycin N=97 n (%)	Ceftriaxone N=92 n (%)		Daptomycin N=272 n (%)	Ceftriaxone N=279 n	
Cure rate	88 (90.7)	81 (88)	2.7 (-6.1%, 11.5%)	205 (75.4)	245 (87.8)	-12.4% (-18.8, -6.0)

[1] Pertel, PE, P Bernardo, C Fogarty et al., 2008, Effects of Prior Effective Therapy on the Efficacy of Daptomycin and Ceftriaxone for the Treatment of Community-Acquired Pneumonia, Clin Infect Dis, 46:1142-51.

The question of whether patients with higher PORT scores are less likely to show an effect of prior antibacterial therapy than patients with lower PORT scores was also explored. For example, in more severely ill patients, do 24 hours or less of prior antibacterial therapy affect clinical response? Analyses of the daptomycin trials revealed that prior antibacterial therapy affects the observed treatment effect even in patients with PORT scores of III or IV.

Future CABP trials

Patient population

This guidance recommends inclusion and exclusion criteria (section III.B.3.) designed to enroll patients with CAP of a bacterial etiology (i.e., CABP) with a set distribution of PORT scores.

This increases the likelihood that the patient population in CABP trials is comparable to that studied historically (pneumococcal or lobar pneumonia).

Age

Age is a strong predictor of mortality in CAP, and from the historical studies and clinical trials of patients with pneumococcal pneumonia there was a larger treatment effect in patients older than 50 years of age. As noted in Table A3, the point estimate for treatment effect approximately doubles in the patient population older than 50 years of age compared to the population younger than 50 years of age. Age is also a large factor in the PORT score, and specifying a population with this distribution of PORT scores as outlined in the guidance will lead to enrollment of a population that is largely older than 50 years of age. Based on these factors, we anticipate the following:

- For an IV drug trial, approximately 75 percent of the population will be 50 years of age or older
- For an oral drug trial, approximately 50 percent of the population will be 50 years of age or older

Thus, CABP trials as described in this guidance should enroll a patient population with lobar disease on chest X ray along with other cardinal signs of pneumonia, a population with the aforementioned distribution of PORT scores, and an age distribution of approximately 75 percent (in IV drug trials) or 50 percent (in oral drug trials) older than 50 years of age.

Comparator agents

Present-day CABP trials should use comparator agents that are FDA-approved for CAP and that are recommended by guidelines to achieve a comparator with a high degree of efficacy. Based upon the finding that prior antimicrobial therapy affected the cure rates in the daptomycin trials, it is critical that the use of prior antibacterial therapy be minimized in the present-day CABP trials. Drug trials for CABP should exclude patients who have received any prior antibacterial therapy.

Most of the available data on treatment effect are data from many years ago and there have been advances in medical care over this time period. Nevertheless, this information provides evidence of treatment effect with antibacterials and allows for reasonable judgments regarding expected treatment effect in a present-day CABP trial. The patient characteristics and trial design factors that are described above are chosen to design a trial that has the capacity to achieve an expected treatment effect.

Noninferiority margin

IV antibacterial drugs

In a patient population enrolled in a present-day CABP trial for an IV formulation as described in this guidance, the treatment effect is likely to exceed that which was observed for the trials described in Table A4 with a lower bound of 8.8 percent, because of: 1) the inclusion criteria; 2) the distribution of PORT scores; 3) the proportion of patients older than 50 years of age; 4) the exclusion of patients with prior antibacterial therapy; and 5) the use of an approved and guideline-recommended comparator antibacterial therapy. The observation that the lower bounds of the 95 percent CI for the treatment effect varied from 15 to 22 percent in the observational studies in patients with pneumococcal pneumonia (Table A1) suggests that there is a larger treatment effect when a bacteriologic diagnosis is made.

The MITT population will be considered the primary analysis population. Use of the MITT population provides reasonable assurance that most of the patients in the trial have a documented microbiologic diagnosis. Thus, based on the evidence discussed in this Appendix, a reasonable estimate of M1 for the MITT population for the endpoint of clinical outcome in a CABP trial is at least 15 percent for patients enrolled in IV antibacterial trials and an M2 of up to 15 percent is considered appropriate in the MITT population.

Oral antibacterial drugs

Oral antibacterial drug trials generally enroll patients with less severe disease than IV antibacterial drug trials, introducing additional uncertainly regarding the antibacterial treatment effect. As described above, the MITT population will be considered the primary analysis population. Use of the MITT population provides reasonable assurance that most of the patients in the trial have a documented microbiologic diagnosis.

In oral antibacterial drug trials, there are greater uncertainties in the treatment effect. Because patients enrolled in such trials can have illness of lesser severity, the magnitude of treatment effect may be smaller. Thus, based on the evidence discussed in this Appendix, a reasonable estimate of M1 for the MITT population for the endpoint of clinical outcome in a CABP trial of oral antibacterial drug is at least 10 percent and an M2 of up to 10 percent is considered appropriate for the MITT population.

For both IV and oral antibacterial drug trials, results in the ITT, clinically evaluable, and microbiologically evaluable populations should be examined for consistency with the results in the MITT population.

Summary

Based on data from historical studies and clinical trials, appropriate noninferiority margins for CABP trials for IV drugs and oral drugs have been described. To arrive at these margins from the available data a series of judgments were required. In addition, the recommended design of

1093 the CABP trials includes a number of provisions to select and evaluate populations that are
1094 appropriate for the proposed margins. These provisions include defining CABP as a clinical
1095 syndrome consistent with bacterial pneumonia and limiting enrollment to an appropriate patient
1096 population based on age, severity of illness, making the MITT the primary analysis population,
1097 and excluding patients who received prior antibacterial therapy.