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DRAFT GUIDANCE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)

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Revision 2

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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development program and clinical trial designs for drugs to support an indication for the treatment of CABP.[2] This draft guidance is intended to serve as a focus for continued comments and discussions among the Division of Anti-Infective Products, pharmaceutical sponsors, the academic community, and the public.[3]

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*, respectively.[4]

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

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

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

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

This guidance revises the draft guidance for industry *Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment* that issued in March 2009. When final, this guidance will be considered the FDA's current thinking regarding the development of drugs for the treatment 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

This guidance provides information to assist sponsors developing drugs for the treatment of CABP. CABP is defined as an acute bacterial infection of the pulmonary parenchyma associated with chest pain, cough, sputum production, difficulty breathing, chills, rigors, fever, or hypotension, and is accompanied by the presence of a new lobar or multilobar infiltrate on a chest radiograph. Common typical bacterial pathogens that cause CABP include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and *Moraxella catarrhalis.* Atypical bacterial pathogens such as *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* also cause CABP.

Changes from the 2009 draft CABP guidance, based on public discussions and comments to the docket, have been incorporated into the appropriate sections below.[5] These changes are intended to attain a greater degree of balance between the practicability of conducting CABP clinical trials and the trial procedures needed for a scientifically sound and interpretable trial.

[5] There have been several public discussions with the FDA regarding CABP. For example: (1) a 2008 Clinical Infectious Diseases supplement that summarized a workshop co-sponsored by the FDA and professional societies, titled "Workshop on Issues in the Design and Conduct of Clinical Trials of Antibacterial Drugs in the Treatment of Community-Acquired Pneumonia" (Clinical Infectious Diseases, December 1, 2008; volume 47 (supplement number 3)); (2) a 2008 Anti-Infective Drugs Advisory Committee (AIDAC) meeting on endpoints and clinical trial design issues for CABP at http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiInfective; (3) the December 9, 2009, AIDAC meeting on CABP issues at http://www.fda.gov/AdvisoryCommittees/Calendar/ucm187911.htm; and (4) the November 3, 2011, AIDAC meeting on CABP clinical trials at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm242307.htm (the November 3, 2011, AIDAC meeting information is at the bottom of the Web page). Notably, this revised guidance provides new efficacy endpoint recommendations (section III.B.8., Efficacy Endpoints), allows enrollment of up to 25 percent of the patient population who have received prior antibacterial drug therapy (section III.B.7., Choice of Comparators, Prior Antibacterial Drug Use, and Concomitant Therapy), and recommends the intent-to-treat population as the primary analysis population (section III.B.10., Statistical Considerations).

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Nonclinical Development Considerations

New antibacterial drugs being studied for CABP should have nonclinical data documenting activity against the commonly implicated pathogens for CABP.

2. Drug Development Population

The trial population should include individuals most likely to have CABP, as defined above, and who can therefore benefit from antibacterial therapy.

3. Efficacy Considerations

Noninferiority trials are interpretable and acceptable to support approval of a drug for an indication for the treatment of CABP. A showing of superiority to an effective control is also readily interpretable and would be acceptable.

Historical data show that antibacterial drugs demonstrate a considerable treatment effect compared to nonantibacterial therapies on clinical responses evaluated during the first 5 days of therapy.

Although it remains important for a trial to demonstrate sustained clinical responses, currently there is insufficient historical evidence to define the treatment effect on endpoints at or after therapy completion. There is adequate information to define a reliable treatment effect on all-cause mortality.

A single adequate and well-controlled trial in CABP supported by evidence of antibacterial activity accrued during a clinical development program (e.g., efficacy in another indication such as acute bacterial skin and skin structure infection; data from a phase 2 clinical trial in CABP) may provide evidence of effectiveness in CABP. Sponsors should discuss their proposed CABP development program with the FDA as well as the other independent evidence that would be used to support the findings from a single trial.[6]

4. Safety Considerations

If the same or greater dose and duration of the drug is used in clinical development for other infectious disease indications, safety data from the other infectious disease indications can be used in an overall safety database to support an indication for CABP. In general, a minimum of 700 patients should be included in the safety database. For new drugs that have an important clinical benefit over existing therapies, depending on the benefit demonstrated, a smaller

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

premarketing safety database may be appropriate. Sponsors should discuss the appropriate size of the premarketing safety database with the FDA during clinical development.

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 except when they are add-on superiority trials in which patients receive either placebo or investigational drug added to standard-of-care antibacterial drug treatment.

2. Trial Population

The trial population for efficacy trials should include patients with CABP based on the entry criteria described in section III.B.3., Entry Criteria. We recommend that at least 75 percent of patients in trials have Pneumonia Patient Outcomes Research Team (PORT) scores of III or higher (Fine, Auble, et al. 1997). For trials in which most patients would be treated as outpatients, sponsors should discuss the trial population and its level of baseline severity with the FDA in advance of a phase 3 trial (e.g., whether the trial may enroll patients with PORT scores of II or higher).

3. Entry Criteria

a. Clinical, radiographic, and microbiologic entry criteria

Sponsors should use entry criteria that select patients who have evidence of a diagnosis of CABP as outlined in Table 1.

Table 1. Summary of Entry Criteria for a CABP Trial

At Least Two Symptoms	**At Least Two Vital Sign Abnormalities**	**At Least One Finding of Other Clinical Signs and Laboratory Abnormalities**	**Chest Radiograph Findings**	**Microbiologic Criteria**
- Difficulty breathing - Cough - Production of purulent sputum - Chest pain	- Fever - Hypotension - Tachycardia - Tachypnea	- Hypoxemia - Clinical evidence of pulmonary consolidation - An elevated total white blood cell count or leukopenia	New infiltrates in a lobar or multilobar distribution	Appropriate sputum specimen: fewer than 10 squamous epithelial cells and more than 25 polymorphonuclear cells per low power field

An adequate specimen of respiratory secretions should be obtained in all patients and should be processed by the laboratory according to recognized methods for Gram stain, culture, and in vitro

antibacterial susceptibility testing performed on appropriate organisms isolated from the specimen.[7]

Bacterial detection methods other than culture may be used to define the microbiological intent-to-treat (micro-ITT) population (see section III.B.10.a., Analysis populations). Such methods may include the following: (1) use of rapid diagnostic tests (e.g., urinary antigen test for *S. pneumoniae*); and (2) nonculture methods of testing (e.g., serology, polymerase chain reaction). Use of rapid diagnostic tests may help to select a patient population with an identified bacterial etiology for CABP.

The clinical trial of an antibacterial drug also may provide an opportunity to contribute to the development and evaluation of a new diagnostic test. Sponsors interested in also using a clinical trial in patients with CABP as a means for the evaluation of a diagnostic test are encouraged to discuss this with the FDA.

b. Exclusion criteria

Exclusion criteria should include the following:

- Aspiration pneumonia
- Hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia
- Patients with known bronchial obstruction or a history of post-obstructive pneumonia (this criterion 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 and Blinding

Patients should be randomized to treatment groups at enrollment. All trials should be double-blind unless there is a compelling reason for not blinding treatment allocation. If trials are single-blind or open-label, sponsors should discuss potential biases with the FDA and how these biases will be addressed.

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

176 *5. Specific Populations*
177
178 The trials should include patients of both sexes and all races, as well as geriatric patients.[8]
179 Patients with renal or hepatic impairment may be enrolled, provided pharmacokinetics of the
180 drug have been evaluated in these patients and appropriate dosing regimens have been defined.
181
182 Sponsors should discuss drug development in the pediatric populations as early as is feasible.
183 The Pediatric Research Equity Act (PREA), as amended by the Food and Drug Administration
184 Safety and Innovation Act, states that initial plans for the conduct of pediatric studies (referred to
185 as an *initial pediatric study plan*) shall be submitted to the FDA before the date on which
186 required pediatric assessments are submitted under PREA and no later than (1) 60 days after the
187 end-of-phase 2 meeting or (2) such other time as may be agreed upon by the FDA and the
188 applicant.[9]
189
190 *6. Dose Selection*
191
192 To choose the dose or doses to be evaluated in phase 3 clinical trials, sponsors should integrate
193 the findings from nonclinical toxicology studies, animal models of infection, pharmacokinetics,
194 safety and tolerability information from phase 1 clinical trials, and safety and efficacy
195 information from phase 2 dose-ranging clinical trials. Trials assessing drug penetration at the
196 site of action (e.g., epithelial lining fluid) may be helpful in defining doses that achieve
197 concentrations sufficient to exert an antibacterial effect. In addition, the pharmacokinetics of the
198 drug in specific populations (e.g., geriatric patients, patients with renal or hepatic impairment)
199 should be evaluated before initiation of phase 3 trials to determine whether dose adjustments are
200 necessary. This evaluation may prevent the exclusion of such patients from phase 3 clinical
201 trials.
202
203 *7. Choice of Comparators, Prior Antibacterial Drug Use, and Concomitant Therapy*
204
205 In general, the active comparator should be considered standard of care for this indication.
206 When evaluating the current standard of care, we consider recommendations by authoritative
207 scientific bodies (e.g., American Thoracic Society, Infectious Diseases Society of America)
208 based on clinical evidence and other reliable information that reflects current clinical practice.
209
210 Ideally, patients enrolled in a CABP clinical trial should not have received prior antibacterial
211 drug therapy because such therapy may have a number of potential consequences for a clinical
212 trial. Prior antibacterial drug therapy could:
213

[8] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers*.

[9] See PREA (Public Law 108-155; section 505B of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 355c) as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (Public Law 112-144) and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

- Obscure true treatment differences between an investigational drug and the control drug introducing bias toward a finding of no difference between treatment groups (i.e., a bias toward noninferiority)[10]

- Particularly influence the efficacy findings based on an endpoint early in therapy (day 3 to day 5)

However, exclusion of all patients who have received prior antibacterial therapy also may pose problems, including:

- Excluding patients with greater disease severity (i.e., patients who received prompt administration of antibacterial drug therapy), which may result in a patient population with lesser severity of illness and greater potential for spontaneous recovery; this could bias trial results toward a finding of no difference between treatment groups (i.e., a bias toward noninferiority)

- Certain trial sites may not participate in the clinical trial because of concerns that trial treatment would not represent standard of care.

A pragmatic approach to these concerns is to: (1) encourage prompt enrollment procedures so that patients can receive the clinical trial treatment initially, with no need for other antibacterial drug therapy; and (2) allow enrollment of some patients who have received a single dose of a short-acting antibacterial drug within 24 hours of enrollment (ideally there would be few such patients but up to 25 percent of the patient population could be allowed). This would permit patients in the trial to receive prompt antibacterial drug therapy as clinically necessary, consistent with the standard of care. The results in the subgroup of patients (i.e., the majority of patients) who did not receive prior effective antibacterial drug therapy would be important to evaluate. The primary analysis should be stratified by prior therapy to assess the consistency of the results across the two subgroups (i.e., patients who received prior therapy and those who did not receive prior therapy).

In general, concomitant antibacterial therapy with an antimicrobial spectrum that overlaps with the spectrum of the investigational drug should not be administered during the trial. We recognize the need in certain circumstances for the empirical coverage against atypical pathogens (e.g., *Legionella* species). The additional antibacterial coverage for atypical pathogens should be discussed with the FDA before trial initiation. The additional antibacterial coverage for atypical pathogens should be promptly discontinued after a determination has been made that CABP is not caused by an atypical pathogen of concern (e.g., a negative test result on a *Legionella* antigen assay).

[10] For example, see Pertel, Bernardo, et al. 2008.

8. Efficacy Endpoints

a. Primary endpoint

The primary efficacy endpoint of clinical success is defined as improvement at day 3 to day 5 in at least two of the following symptoms: chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing.[11] Symptoms should be evaluated on a four-point scale (absent, mild, moderate, severe) with improvement defined as at least a one-point improvement from baseline to the assessment at day 3 to day 5 (e.g., from severe to moderate, from moderate to absent, or from mild to absent).[12]

An endpoint of all-cause mortality at 28 days after enrollment may be used as a primary efficacy endpoint in CABP clinical trials in certain patient populations. However, sponsors considering the use of all-cause mortality as the primary efficacy endpoint should discuss the trial design with the FDA.

b. Secondary endpoints

Sponsors should evaluate the following as secondary endpoints:

- Improvement at day 3 to day 5 in at least two of the following symptoms with no worsening in any of these symptoms of CABP compared to baseline: chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing; *and* improvement in vital signs (i.e., body temperature, blood pressure, heart rate, respiratory rate).[13]

- Clinical outcome at the end of therapy.

- Clinical outcome at a fixed time point after therapy completion. Patients with resolution of symptoms and signs attributable to CABP at 5 to 10 days following completion of treatment and who did not receive nontrial antibacterial drugs for treatment of CABP should be considered successes on this secondary endpoint.

Other examples of secondary endpoints for consideration are as follows:

- Changes in white blood cell counts from baseline to day 3 to day 5
- Changes in oxygenation from baseline to day 3 to day 5

[11] See Talbot, Powers, et al. 2012.

[12] See Toerner, Burke, et al. 2012. For information regarding the development of patient-reported outcome measures, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

[13] Improvement or stabilization of vital signs and other signs attributable to CABP should be defined in the protocol. For example, see table 10 in Mandel, Wunderink, et al. 2007.

c. IV and oral formulations

For drugs that have only an intravenous (IV) formulation available, sponsors should conduct trials with the IV formulation alone until the day 3 to day 5 efficacy endpoint assessment is complete, if feasible, to allow for assessment of both the efficacy and safety of the investigational drug. Assessment of the primary endpoint at day 3 to day 5 before switching to an oral antibacterial drug should ensure that the evaluation of efficacy reflects the effects of the investigational IV drug. The overall duration of antibacterial drug therapy (i.e., days of IV therapy plus days of oral drug therapy) should not involve an unnecessarily long course of oral switch therapy, so that the contribution of the IV investigational drug to overall efficacy on secondary endpoints at 5 to 10 days after completion of treatment can be assessed.

For drugs that have both an IV and oral formulation, the protocol should specify the criteria that allow for IV-to-oral switch. The sponsor should collect pharmacokinetic (PK) data for IV and oral formulations in earlier phase studies to select the appropriate oral dose for the IV-to-oral switch.

9. Trial Procedures and Timing of Assessments

a. Entry visit

The following information should be captured at the entry visit (see section III.B.3., Entry Criteria, and section III.B.8., Efficacy Endpoints):

- Appropriate demographic information
- History and physical examination findings
- Prior medication use
- Baseline assessments of symptoms
- Baseline assessments of clinical signs of CABP
- Baseline appropriate laboratory tests
- Chest radiographic findings
- Microbiological specimens
- Severity scores

b. On-therapy visits

Investigators should document findings from on-therapy clinical trial visits (e.g., history, physical examination, adverse effects, laboratory test results). Patients should be evaluated for the symptoms of chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing at day 3 to day 5. Patients also should be evaluated at the end of therapy.

c. After therapy visit

At this visit at 5 to 10 days after completion of treatment, sponsors should capture physical examination findings, assessments of symptoms, assessments of signs, assessments and

resolution of adverse effects, if any, and appropriate laboratory tests. Patients should be evaluated at day 28 for assessment of all-cause mortality.

10. Statistical Considerations

The trial hypotheses and the analysis methods should be prespecified in the protocol and in the statistical analysis plan, and should be finalized before trial initiation.[14]

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.
- Intent-to-treat (ITT) population — All patients who were randomized.
- Micro-ITT population — All randomized patients who have a baseline bacterial pathogen known to cause CABP against which the investigational drug has antibacterial activity. This includes bacterial pathogens identified by standard culture methods of an appropriate sputum specimen or blood. Recently conducted trials suggest that approximately 25 percent of the ITT population will have bacterial pathogens identified by standard culture methods. In addition, nonculture methods of detection of bacterial pathogens (e.g., urinary antigen test) may be used to identify patients for inclusion in a micro-ITT analysis population.
- 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 micro-ITT population and who follow important components of the trial as specified in the protocol.

Sponsors should discuss with the FDA the prespecified primary analysis population in advance of trial initiation. The ITT population may be considered as the primary analysis population when (1) the trial enrolls patients who are most likely to have a bacterial etiology for pneumonia and (2) the investigational antibacterial drug can be administered as monotherapy that has antibacterial activity against the typical bacterial pathogens that cause CABP.[15]

The ITT population is likely to have a substantial fraction of patients who do not have a bacterial pathogen identified on sputum culture. Nonetheless, the ITT population (i.e., patients who meet

[14] See ICH E9 and ICH E10, and the draft guidance for industry *Non-Inferiority Clinical Trials* (when final, this guidance will represent the FDA's current thinking on this topic).

[15] The micro-ITT population is an important analysis population, in particular if the investigational antibacterial drug has a narrow spectrum of activity (e.g., a drug active against a single genus and species of bacteria).

the inclusion criteria described in section III.B.3, Entry Criteria) may be informative based on observations from previously conducted trials and evaluations. For instance, among patients who did not receive prior therapy in a trial in which there was an observed treatment difference between two antibacterial drugs (Pertel, Bernardo, et al. 2008), the subgroup of patients who did not have a positive sputum culture for a bacterial pathogen showed a treatment difference similar to the treatment difference among the subgroup of patients with a positive culture. This indicates a strong likelihood that the patients enrolled in this trial without a positive sputum culture actually had bacterial disease (Rubin, Toerner, et al. 2012). In addition, extensive nonculture methods performed in a research setting from sputum specimens identified a possible bacterial etiology for pneumonia in some patients who did not have a bacterial pathogen identified on a sputum or blood culture (Johansson, Kalin, et al. 2010). Another evaluation of patients with pneumonia who did not have a bacterial pathogen identified on a sputum or blood culture found that a more invasive search can identify a bacterial etiology in a large proportion of patients (Ruiz-González, Falguera, et al. 1999).

However, sponsors planning to develop a drug for the sole indication of the treatment of CABP should consider conducting two adequate and well-controlled trials of identical design. Each of these trials could potentially be powered based on the ITT population of that trial. Further, a noninferiority efficacy analysis in a micro-ITT population could potentially use data pooled from both trials. Sponsors planning to conduct a single CABP trial, with other supportive data, to support approval for CABP should discuss this plan with the FDA in advance and are encouraged to submit a special protocol assessment.[16]

The micro-ITT population should allow a sufficient description of baseline microbiological findings for adequate labeling information.

b. Noninferiority margins

Historical experience indicates that there is a relatively large treatment effect of antibacterial therapy on clinical recovery at day 3 to day 5 (see the Appendix). In general, the selection of a noninferiority margin (M_2) of 12.5 percent is reasonable for CABP clinical trials using a clinical recovery endpoint at day 3 to day 5. In certain circumstances (e.g., a narrow spectrum drug for a limited population with unmet medical need), it may be reasonable to consider a noninferiority margin greater than 12.5 percent. Sponsors should discuss with the FDA a clinically appropriate noninferiority margin in advance of trial initiation.

c. Sample size considerations

A general framework is provided for sponsors to begin to discuss sample size considerations with the FDA during protocol development. In this illustrative sample size calculation, approximately 225 patients per group is estimated based on the following assumptions: (1) a rate of clinical success for the active-controlled therapy of 80 percent; (2) two-sided type I error (α) of 0.05; (3) type II error (β) of 0.10 (power 0.90); (4) a noninferiority margin of 12.5 percent (see the Appendix); and (5) an ITT analysis population.

[16] See the guidance for industry *Special Protocol Assessment*.

11. Risk-Benefit Considerations

Risk-benefit considerations may depend on the population being studied. For example, for an IV-administered antibacterial drug targeted for treatment of hospitalized patients seriously ill with CABP, certain types of adverse effects that can be monitored in a hospital setting might result in a risk-benefit consideration that is appropriate, while such adverse effects might result in a risk-benefit consideration that is not appropriate for an orally administered antibacterial drug targeted for treatment of mildly ill outpatients.

C. Other Considerations

1. Pharmacokinetic/Pharmacodynamic Evaluation

The PK/pharmacodynamic (PD) characteristics of the drug should be evaluated using in vitro methods and animal models of infection.

The limitations of *S. pneumoniae* pneumonia and *H. influenzae* pneumonia animal models, when considering their implications for humans, include the differences among the animal models in the mode of infection and in the reproducibility of infection (Tessier, Kim, et al. 2002; Gavalda, Capdevila, et al. 1997; Legget 1999; Miyazaki, Nunoya, et al. 1997), and differences in the effect of animal lung secretions versus human lung secretions on the activity of the antibacterial drug (Silverman, Mortin, et al. 2005). Animal studies are not a substitute for clinical trials in patients with CABP.[17]

The PK/PD characteristics of the drug (including the relationships to the minimum inhibitory concentrations) should be integrated with the findings from phase 1 PK clinical trials to help identify appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical trials. A dose-response trial may be considered as an option for clinical trials early in development to weigh risks and benefits when selecting doses and to ensure that suboptimal doses or excessive doses (beyond those that add to efficacy) are not used in the phase 3 trial, offering some protection against unexpected and unrecognized dose-related toxicity.[18]

Sponsors should consider obtaining blood samples from all patients in phase 2 and phase 3 clinical trials (*sparse sampling*) to allow for the estimation of drug exposure in each patient. A retrospective exposure-response analysis based on the population PK model should be performed to assess the relationship between exposure and observed clinical and microbiologic outcomes. The relationship between drug exposure and clinically relevant adverse events also should be explored to identify potential risks with different dosing regimens (if applicable) and specific patient populations.

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

[18] 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*.

2. Labeling Considerations

Generally, the labeled indication should be the treatment of CABP caused by the specific bacteria identified in a sufficient number of patients in the clinical trials and should reflect the patient population enrolled in the clinical trials.

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APPENDIX:
NONINFERIORITY MARGIN JUSTIFICATION FOR CABP

Background

The selection of a noninferiority margin depends on a reliable estimate of the treatment effect of the active comparator (i.e., effect of the active comparator over placebo, referred to as M_1), usually based upon placebo-controlled trials, that can be assumed to hold for the noninferiority trial. After M_1 is established, clinical judgment determines how much of the estimated treatment effect (M_1) should be preserved in determining a clinically acceptable noninferiority margin, referred to as M_2.

Historical studies and clinical trials of antibacterial treatment of bacterial pneumonia provide evidence that antibacterial drugs have the following effects:

- Achievement of a greater proportion of patients with favorable clinical responses at time points earlier in the course of antibacterial drug therapy (i.e., at day 3 to day 5)

- Reduction of mortality in patients with pneumococcal or lobar pneumonia

An area of uncertainty in evaluating historical data is the spectrum of bacterial pathogens that cause CABP today. In most of the historical studies and historical-controlled clinical trials, CABP was considered synonymous with pneumococcal pneumonia because *S. pneumoniae* was regularly identified. A review of recently conducted trials showed that less than 20 percent of the total patient populations had documented *S. pneumoniae* (Higgins, Singer, et al. 2008). CABP is also caused by other pathogens such as *H. influenzae*, *H. parainfluenzae*, *S. aureus*, and *M. catarrhalis*, as well as atypical bacteria such as *M. pneumoniae*, *C. pneumoniae*, and *Legionella* species. Limited information is available on antibacterial treatment effect in CABP caused by *M. pneumoniae* (Kingston, Chanock, et al. 1961). A fundamental assumption is that historical response rates in infections such as *S. pneumoniae* CABP are relevant to response rates in modern infections with sensitive organisms.

We describe the steps taken to determine a noninferiority margin for two primary outcome measures: (1) an endpoint based on the outcome assessments of chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing; and (2) all-cause mortality endpoint.

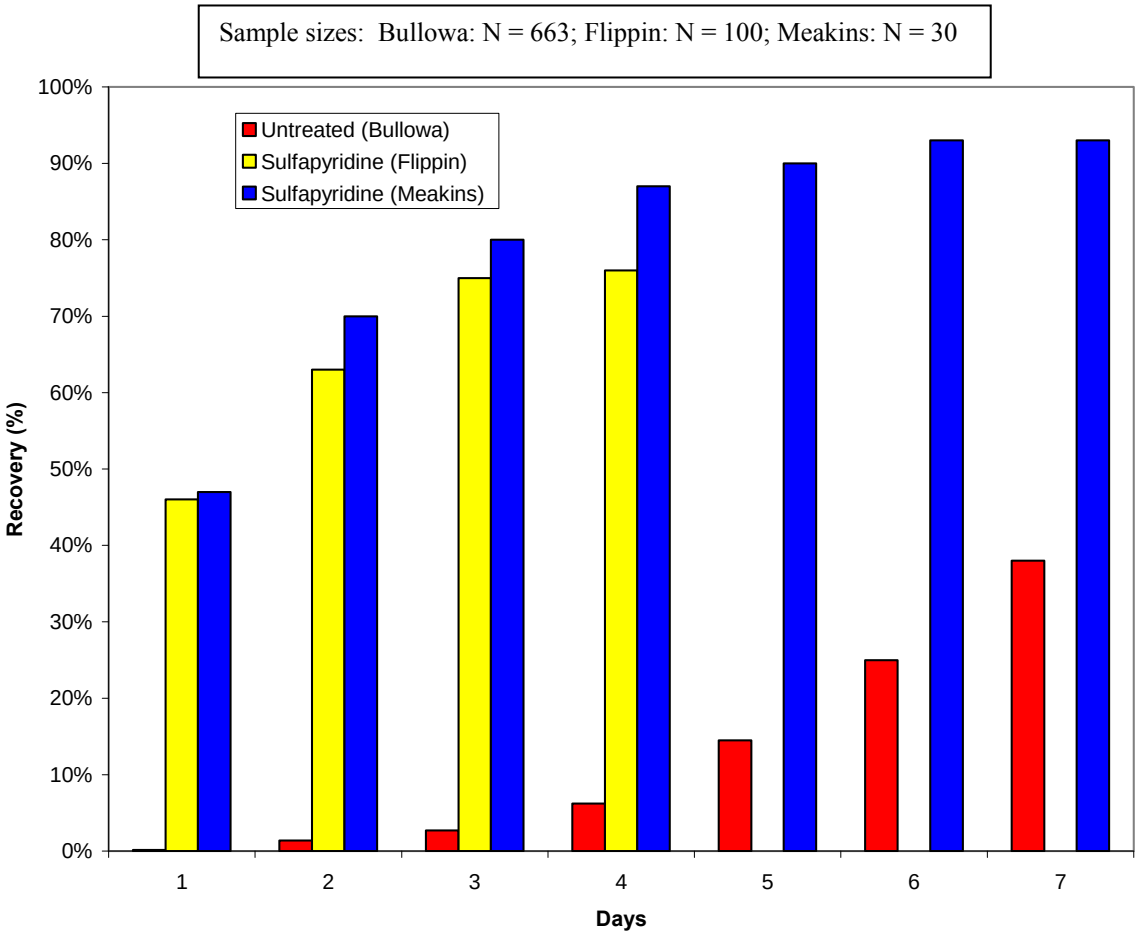
1. Endpoint Based on Clinical Outcome Assessments at Day 3 to Day 5 After Enrollment

Studies conducted around the time of the introduction of antibacterial drug therapy described clinical responses among untreated patients and patients treated with antibacterial drugs. These observational studies provide an estimate of the effect of antibacterial drugs on clinical response endpoints other than mortality.

Several papers described the clinical course of patients with pneumococcal pneumonia in a similar way; patients were recorded as having a successful clinical result by the demonstration of

fever resolution and accompanying improvement and resolution of other signs and symptoms of pneumonia. For example, a description in one of the papers stated, "This fall in temperature was in all cases accompanied by a conspicuous reduction in the pulse and respiratory rates, and the patients were improved subjectively" (Meakins and Hanson 1939). One study described the clinical course of 663 patients who did not receive antibacterial drug therapy (Bullowa 1937), while two other studies included patients who received antibacterial drug therapy. One study described the clinical course in 100 patients with pneumococcal pneumonia (Flippin, Lockwood, et al. 1939) and another study described the clinical course in 30 patients with pneumococcal pneumonia (Meakins and Hanson 1939). Figure A compares the three studies in the rates of clinical recovery, defined generally as the improvement in both clinical signs and symptoms.

Figure A. Rates of Clinical Recovery Recorded at Each Day

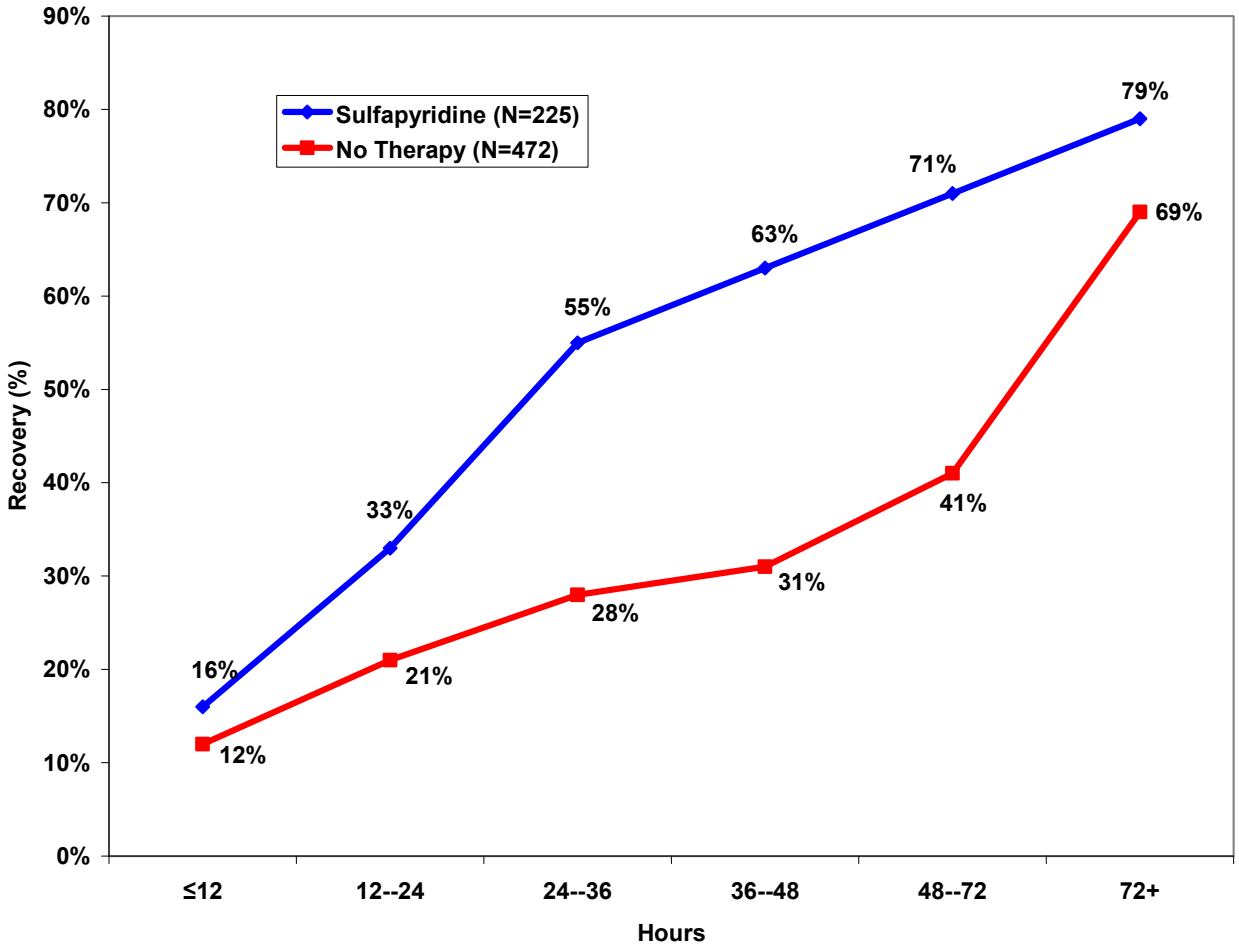


The difference in clinical recovery rates between patients in the two treatment studies and patients in the study without treatment were 72 percent and 77 percent.

Figure B shows the rates of clinical recovery in an observational study of patients with pneumococcal pneumonia who received antibacterial drug therapy (sulfapyridine) and a group of patients who received no specific therapy. Clinical recovery was defined as "permanent drop in

oral temperature below 100°F, with subsidence of other symptoms of acute infection" (Finland, Spring, et al. 1940). Time points at 36 to 48 hours and 48 to 72 hours after therapy initiation demonstrate the greatest treatment effect of clinical recovery. The treatment difference is approximately 30 percent (95 percent confidence interval: 22 percent, 37 percent) at the 48- to 72-hour time point. Clinical observations that were reported at any time after the 48- to 72-hour assessment are displayed as *72+* in Figure B. The time points after 72 hours (i.e., 72+) included recovery time points out to several weeks following therapy completion.

Figure B. Rates of Clinical Recovery of Acute Bacterial Pneumonia (Finland, Spring, et al. 1940)



Another paper described the outcomes among pediatric patients with pneumococcal pneumonia and provides additional support for a treatment effect of antibacterial drugs relatively early in therapy. The mean time to clinical recovery was 4.7 days among patients who received antibacterial drug therapy while patients who did not receive antibacterial drug therapy had a mean time to clinical recovery of 8.9 days (Wilson, Spreen, et al. 1939).

The clinical response endpoints that were evaluated in each of these studies were not well defined. The studies evaluated both signs and symptoms together. A large treatment effect was observed at the early time point in the course of therapy (i.e., day 3 to day 5 after therapy

initiation) for an endpoint that included improvement in both signs and symptoms. The studies show that the treatment differences become smaller at times beyond day 3 to day 5 of therapy. Aspects that support the use of these studies as an estimate of M_1 include the following:

- The studies documented bacterial pneumonia, all as *S. pneumoniae*.
- The estimate of the treatment difference appears to be large and is consistent across studies.
- Some patients included in the *no therapy* group in Figure B were patients who had signs and symptoms of milder pneumonia. Even after the availability of antibacterial drugs, the clinician chose not to treat such patients with antibacterial drug therapy because of the likelihood of spontaneous recovery. The inclusion of patients more likely to experience spontaneous recovery of pneumonia in the no therapy group leads to an underestimate of the true treatment difference among patients with more serious disease.
- The clinical response measurements are plausible consequences of treating an infection.

The limitations of these studies include the following:

- The studies were not randomized
- Historically controlled studies create a greater level of uncertainty in the estimate of treatment differences
- The clinical response evaluations were not defined
- The clinical response evaluations included improvement in both signs and symptoms together and did not separately evaluate improvement in chest pain, frequency or severity of cough, amount of productive sputum, and difficulty breathing

The treatment difference appears to be large for an endpoint based on clinical outcome assessments earlier in the course of therapy for CABP. However, the results are variable, ranging from the point estimate of 30 percent treatment difference at a 48- to 72-hour time point noted in Figure B to a point estimate of 77 percent treatment difference at day 3 noted in Figure A.

It is difficult to provide a precise numerical value for the treatment effect of a proposed primary endpoint of symptom improvement at day 3 to day 5. However, an M_1 of at least 20 percent appears to be a reasonably appropriate and conservative estimate, accounting for the uncertainties with clinical recovery in the historical literature. A conservative estimate of M_1 at 20 percent is still large enough to support the selection of a noninferiority margin (M_2) of 12.5 percent for the endpoint of symptom improvement at day 3 to day 5. The selection of the noninferiority margin (M_2) is a matter of clinical judgment and should be justified by the sponsor.

2. All-Cause Mortality Endpoint

Table A provides an overview of the types of historical data used to support the identification of a treatment effect based on all-cause mortality.

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

Publication	Population	Mortality (%) Untreated (Study Years)	Mortality (%) Antibacterial-Treated (Study Years)	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)	18.2% (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, Nambiar, et al. 2008
[2] Finland 1943
[3] Dowling and Lepper 1951
[4] Austrian and Gold 1964
* Historical controls

The lower bounds of the 95 percent confidence interval for the treatment effect varied from 15 to 41 percent in the observational studies in patients with pneumococcal pneumonia. Thus, a conservative estimate of M_1 for the endpoint of all-cause mortality in a CABP trial is at least 15 percent.

Summary

Based on data from historical studies and clinical trials, appropriate approaches to selecting noninferiority margins for CABP trials have been described. The available data support a noninferiority margin justification for two efficacy outcome assessments:

1. An endpoint based on symptom improvement at day 3 to day 5 compared to baseline

2. All-cause mortality endpoint