Guidance for Industry

Community-Acquired Pneumonia — Developing Antimicrobial 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DRAFT GUIDANCE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)
July 1998
Clin-Anti

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7/21/98

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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Community-Acquired Pneumonia — Developing Antimicrobial Drugs for Treatment

I. INTRODUCTION

This is one in a series of guidance documents intended to assist the pharmaceutical industry in the development of antimicrobial drug products for the treatment of infections. The information presented here should help applicants plan clinical studies, design clinical protocol(s), implement and appropriately monitor the conduct of clinical studies, collect relevant data for analysis, and perform appropriate types and numbers of analyses of study data. Clinical trials planned and conducted as recommended in this guidance should yield the information necessary for the Agency to determine whether the antimicrobial under study is safe and effective in the treatment of the specific infection. For general information on related topics, the reader is referred to the guidance *Developing Antimicrobial Drugs — General Considerations for Clinical Trials* (*General Considerations*).

This guidance for industry focuses on developing antimicrobial drugs for the treatment of community-acquired pneumonia; it does not address the study of viral, parasitic, or fungal pneumonia.

II. BACKGROUND

Over the years, the Agency has issued guidance to the pharmaceutical industry on how to design, carry out, and analyze the results of clinical trials for the development of antimicrobials for the treatment of infections in a variety of forms. Guidance has been provided verbally during various industry and FDA meetings, in letters written to sponsors, and in general guidance on related issues. This guidance is the result of efforts to collect all pertinent information and present it in

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[1] This guidance has been prepared by the Office of Drug Evaluation IV, representing the Division of Anti-Infective Drug Products, the Division of Special Pathogens and Immunological Drug Products, and the Division of Anti-Viral Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on developing antimicrobial drugs for the treatment of community-acquired pneumonia. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

one location. Where appropriate, this guidance contains relevant information from several sources, including *Clinical Evaluation of Anti-Infective Drugs (Systemic)* (1977); IDSA's "Guidelines for the Evaluation of Anti-Infective Drug Products" (1992) (IDSA guidance);[2] *Points to Consider: Clinical Development and Labeling of Anti-Infective Drug Products* (1992) (*Points to Consider*), an FDA guidance on issues related to evaluating new drug applications for anti-infective drug products; and *Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products* (February 1997), a draft guidance discussed at a March 1997 advisory committee meeting on anti-infective drug products, which will be superseded by this guidance once it is issued in final form.

III. COMMUNITY-ACQUIRED PNEUMONIA

A. Regulatory Synonyms

Before the indications of *community-acquired pneumonia* and *nosocomial pneumonia* were identified in the 1992 *Points to Consider* documents, patients with these conditions were generally studied under and included in the indication *lower* respiratory tract infections.

B. Study Considerations

1. Study Characteristics

A statistically adequate and well-controlled multicenter trial should be conducted that establishes safety and effectiveness (i.e., similar or superior effectiveness to an approved product) in which the primary effectiveness endpoints should be clinical and radiographic endpoints. Microbiologic evaluations (culture and Gram's stain) should also be performed on each patient. Isolation of a pathogen from the baseline sputum culture should not be required for overall evaluability; however, rigid case definitions, including specific entry sputum microscopy and radiographic findings, specific to the type(s) of community-acquired pneumonia being studied, should be included in the trial design.

Patients should be analyzed in two separate groups: (1) those who were clinically evaluable (whether or not microbiologically evaluable) and (2) those who were clinically evaluable and microbiologically evaluable. Analyses of the data should also generally confirm (by means of comparing the direction of the independent 95% confidence intervals testing) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients. Likewise, the analyses

[2] This guidance appeared in IDSA's (Infectious Disease Society of America) supplement to *Clinical Infectious Diseases*, formerly *Reviews of Infectious Diseases.*

should establish the correlation between clinical cure and bacterial eradication in the clinically and microbiologically evaluable subset of patients.

In addition, a study should be conducted, which may be an open trial, involving at least two investigators in different geographic areas (no one center contributing more than 55% of the evaluable patients) in which 80 evaluable patients are studied. In this trial, the microbiologic etiology of the pneumonia should be confirmed for each patient. For this trial, the applicant should demonstrate that the patient demographics, the disease severity, the exclusion/inclusion criteria, the evaluability criteria, and the effectiveness parameters were not substantively different from those in the adequate and well-controlled first trial. The trial should be performed by different investigator(s) than those involved in the first trial, and the site(s) should represent geographically different area(s). The results of this trial should be consistent with the results obtained in the controlled trial and demonstrate consistency in the action of the drug in treating this infection.

In situations where atypical microorganisms causing community-acquired pneumonia are evaluated or when different susceptibility patterns are expected for specific microorganisms in different populations, different comparative agents and/or different patient populations may be selected that should corroborate one another in the establishment of effectiveness in treating this infection. Analyses of the data should confirm the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients (by comparing the direction of the independent 95% confidence interval testing or by appropriate other analysis if the subgroups can be combined from the two separate studies).

2. Disease Definition:

Community-acquired pneumonia (CAP) in an immunocompetent adult patient is defined as an acute infection of the pulmonary parenchyma that is 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 rates). The patient should not have been hospitalized or resided in a long-term-care facility for $\geq$14 days before the onset of symptoms.[3]

Various combinations of clinical, radiographic, and laboratory criteria are used by clinicians and academicians to diagnose pneumonia. For the purposes of the evaluation of clinical trials, there should be supportive evidence in each of these areas. The clinical entity of *pneumonia* may manifest in a variety of ways given the spectrum of organisms

[3] Bartlett, J. G., et al., "Community-Acquired Pneumonia in Adults: Guidelines for Management," *Clinical Infectious Diseases* 1998;26-811-38.

and host conditions to be considered. The six categories of pneumonia outlined in the 1992 IDSA guidance for inclusion criteria for enrollment and/or stratification of patients who are febrile and have radiographic evidence of pulmonary infiltrates are as follows:

- Atypical pneumonia
- Viral pneumonia
- Acute bacterial pneumonia
- Aspiration pneumonia
- Ventilator-associated pneumonia
- Pneumonia in an immunocompromised and/or neutropenic host

Though the health care environment is rapidly changing, for the most part, cases of atypical pneumonia and viral pneumonia may still be community-acquired (and treated), while those of aspiration pneumonia and ventilator-associated pneumonia may be nosocomial infections. The entity *acute bacterial pneumonia* could be acquired and treated in either setting, but many of these patients may be hospitalized for at least part of their treatment course, thereby adding more challenges to the design, conduct, and evaluation of a clinical trial.

C. Inclusion Criteria

The diagnosis of community-acquired bacterial pneumonia in *adults* should be based on the clinical, radiograph, and microbiologic criteria listed below:

1. Clinical Findings

As part of the clinical picture of community-acquired bacterial pneumonia, a patient should have at least two of the following signs and symptoms:

- Cough
- Production of purulent sputum or a change in the character of sputum
- Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony)

- Dyspnea or tachypnea, particularly if any or all of these are progressive in nature

- Fever, defined as body temperature >38°C (100.4°F) taken orally; >38.5°C (101.2°F) tympanically; or >39°C (102.2°F) rectally *or* hypothermia, defined as core body temperature of <35°C (95°F).

  Note: Some patients, especially elderly and others who have risk factors such as alcoholism, malnutrition, and other comorbid illnesses, develop hypothermia as a sign of infection.

- An elevated total peripheral white blood cell count (WBC>10,000/mm^3); or >15% immature neutrophils (bands), regardless of total peripheral white count; or leukopenia with total WBC < 4500/mm^3.

- Hypoxemia with a PO_2 <60mm Hg while patient is breathing on room air.

To establish the diagnosis of bacterial pneumonia for *pediatric* patients, most of the same diagnostic criteria listed above may be used, with the following exeptions:

- Because pediatric patients may not produce a sputum specimen for culture, blood cultures or serology may be substituted to identify the etiologic bacterial pathogen.

- In infants age 3 to 24 months, who tend to have a higher baseline temperature, fever is defined as a rectal temperature ≥38.3°C (101°F). In children >2 years, fever is more commonly defined as a rectal temperature >38°C (100.4°F).

- In pediatric patients, elevations of WBC counts >15,000/mm^3 are frequent but could be variable in patients with bacterial pneumonia, or leukopenia with WBC count <5000/mm^3; usually associated with severe infection.

2. Radiographic Findings

Within 48 hours prior to institution of therapy, the chest radiograph should show the presence of a new infiltrate(s) in conjunction with the clinical and microbiological findings necessary to establish the diagnosis.

The state of hydration of the patient at the time of the initial radiograph should be taken into consideration. Repeat films after hydration or diuresis are acceptable provided they are taken within the above frame time.

The final full report of the pretreatment chest radiograph by the radiologist should be entered in the case report form.

3. Microbiological Criteria

At the time of enrollment, all patients should have a specimen of respiratory secretions obtained and sent to the laboratory for Gram's stain and semiquantitative culture. The specimen of respiratory secretions may be obtained by any of the following means:

- deep expectoration
- nasotracheal aspiration
- bronchoscopy with bronchoalveolar lavage or protected-brush sampling
- transtracheal aspiration.

The Gram's stain should be performed and the specimen plated for culture within 2 hours from the collection time, if the specimen is kept at room temperature. Alternatively, these tests may be performed within 24 hours of collection if the specimen is stored at 4°C before processing.

Microscopic examination of the Gram-stained respiratory secretions (10-20 oil fields) should show presence of microorganisms and <10 squamous epithelial cells and >25 polymorphonuclear cells per field at 100X magnification (low-power, 10X objective) for suitability of culture.

Any pathogen isolated from the respiratory specimen culture should be tested for antimicrobial susceptibility to the study drugs.

Isolation by culture is preferred for the diagnosis of pneumonia due to *Mycoplasma pneumoniae, Legionella pneumophila,* or *Chlamydia pneumoniae.* Alternative diagnostic tests may be used to establish infection with one of these pathogens. However, due to rapid advances in technology, use of other diagnostic tests should be discussed with the division prior to initiation of the study. In general, a serologic result would be considered positive and establish the microbiological diagnosis if a single IgM diagnostic antibody titer is obtained or if a fourfold increase in IgG titers is obtained in paired serum samples for the pathogen under study.

To be microbiologically evaluable, a bacterial organism consistent with a respiratory pathogen should be isolated from the respiratory secretions.

D. Exclusion Criteria

(See *General Considerations*)

In addition to complying with general exclusion criteria applicable to other trials, patients enrolled in pneumonia trials should be excluded for the following reasons:

1. Patients with known bronchial obstruction or a history of postobstructive pneumonia. (This does not exclude patients who have chronic obstructive pulmonary disease.)

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

3. Unless the study is specifically designed for such a patient population, patients with cystic fibrosis, AIDS, known or suspected *Pneumocystis carinii* pneumonia, or known or suspected active tuberculosis.

E. Drug and Dosing Regimens

Patients should receive treatment for at least 48 to 72 hours (in the absence of an adverse event or other extenuating circumstances necessitating drug discontinuation) before the clinical assessment of failure can be made and at least 5 days of therapy with $\geq$80% compliance for an assessment of a favorable clinical outcome.

Depending on the specific agent, the proposed duration of therapy may vary; however, the specific dose regimen and duration should be clearly stated in the protocol. In general, 5 to 10 days of therapy are advocated for the treatment of outpatients with common bacterial pneumonias. On the other hand, there are recognizable exceptions to these time frames. Pneumonias due to Mycoplasma pneumoniae or *Chlamydia pneumoniae* are typically treated on an outpatient basis for 10 to 14 days. In the recent IDSA *Guidelines for Management of CAP*, it is recommended that treatment for *Mycoplasma pneumoniae* pneumonia and *Chlamydia pneumoniae* pneumonia should be given for 14 to 21 days (2 to 3 weeks) to reduce the risk of relapse, thus this information should be considered when designing a clinical protocol. Patients with Legionnaires' disease are often hospitalized and treated with a 14- to 21-day course.

Finally, if there are provisions to start treatment with a parenteral agent and switch to an oral antimicrobial agent at some point during the course of therapy, this plan should be stated in the protocol. Information should be provided on the criteria patients need to meet to be converted from parenteral to oral therapy, as well as the clinical and other procedures that will be conducted to document the change in the patient's condition that justifies the conversion.

F. Evaluation Visits

The following signs, symptoms, and laboratory data should be evaluated at each visit.

- Temperature
- Peripheral white blood cell count (WBC)
- Respiratory rate (not a valid parameter if patient is on a ventilator)

  Note: The Panel of the 1998 IDSA *Guidelines for Management of CAP* in adults endorses that a respiratory rate of ≥30/min (findings of the Pneumonia Patient Outcomes Research Team (PORT) studies) is one of the valid predictors for mortality. It also endorses the use of this observation for rational decision making regarding hospitalization.

- Sputum quality
- Sputum production
- Severity of cough
- Pleuritic chest pain
- Rigors or shaking chills (if present either initially or after therapy initiated)
- Oxygenation (pulse oximetry or arterial blood gas determinations)
- Chest radiograph appearance
- Gram's stain
- Culture and susceptibility

1. Pretherapy

Patients should have documentation of their pretherapy evaluation, including results of their history and physical examination, and of the signs and symptoms listed above. Depending on the particular protocol, a baseline oxygen saturation reading by pulse oximetry or an arterial blood gas may be used as well.

2. On-Therapy

Outpatients and hospitalized patients should have clinical assessments captured in the case report form. If clinical conditions warrant daily assessments, the results of these should be recorded in the case report forms.

The laboratory assessments to be made during the course of the study can be individualized somewhat for the antimicrobial agent and causative respiratory pathogen under study. However, some general principles follows:

- Cultures of respiratory tract secretions and susceptibility testing of respiratory pathogens, if obtainable, should be repeated 48 to 72 hours after initiation of

therapy in all patients or in patients who are clinically failing to respond to treatment.

- Blood cultures and susceptibility testing should be repeated 48 to 72 hours after initiation of therapy if positive at entry or if the patient is failing to respond to treatment. (Note: Blood cultures are done only in hospitalized patients and pediatric patients.)

- The collection of specimens using semi-invasive techniques (e.g., collection of pleural fluid, transtracheal aspiration, bronchoscopy) is not recommended unless warranted because of a suboptimal clinical response.

At any time while on therapy, a patient may be withdrawn from the study if, in the opinion of the investigator, continuing therapy would jeopardize the patient's health or safety. However, the criteria for early drug discontinuation/withdrawal and how such patients should be handled should be defined *a priori.*

4. End-of-Therapy

An end-of-therapy assessment visit is optional for the purposes of study. Such a visit should not be substituted in lieu of the test-of-cure visit.

5. Early Post-Therapy

Follow-up cultures and laboratory testing are suggested within 72 hours of completion of therapy. Studies done within this visit could be considered to be end of therapy or done to fulfill the goals of the short-term follow-up visit, but are not sufficiently removed from the course of therapy to assess the clinical efficacy of the drug product. If patients have adhered to the drug regimen and failed to respond to a treatment by this point, they can be considered clinical failures.

The timing of the short- and long-term follow-up visits proposed for the assessment of clinical efficacy should be based upon the half-life of the drugs and the natural history of the disease entity under study. Protocols employing drugs with very long half-lives, abbreviated courses of therapy, different durations of therapy between study drug and comparator agent, or any combination thereof, should be reviewed with the division prior to study initiation.

The investigator's assessment at each visit as well as the applicant's assessment at each visit are important. If the applicant's assessment differs from the investigator's, an explanation for the difference should be provided.

6. Test-of-Cure

The findings from the test-of-cure visit, in conjunction with information from earlier visits, are used to determine the clinical and microbiological (when available) efficacy of the antimicrobial drugs under study. This visit should take place at least 7 days after the completion of therapy, assuming the study drugs have a short half-life. The visit should also take place no later than three weeks from completion of treatment unless the drug under study has a particularly long half-life.

At this visit, patients should have documentation of clinical assessments, including results of the physical examination, chest x-ray, and laboratory tests depending on the protocol being studied, as listed above. During this visit, repeat semiquantitative culture and susceptibility testing of sputum and/or respiratory secretion should be done in patients who have continuous sputum production to monitor the emergence of resistance.

G. Outcome

1. Clinical Outcome

Clinical outcome is the primary efficacy variable for the indication of bacterial pneumonia. The patient's response to therapy should be based on a comparison of the patient's baseline signs and symptoms and other laboratory parameters to the patient's evaluation at the post-therapy visit or test-of-cure visit. All failures should be carried forward at the test-of-cure visits.

The patients should meet the inclusion and exclusion criteria, should complete a full course of therapy and receive no additional antimicrobial therapy, and should return for the appropriate study visits.

Patients who have adequate clinical data, but incomplete or inadequate microbiologic data, should be considered to be *clinically evaluable* only.

Clinical outcome should be defined as follows:

a. *Clinical Cure*: Complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on chest radiograph as assessed by the 7- to 21-day test-of-cure visit.

b. *Clinical Failure*: The patient should be considered to have failed therapy under the following conditions:

- Persistence or worsening in signs or symptoms of the acute process after 3 to 5 days of therapy

- Failure to show improvement in at least three of the clinical findings after 3 days of therapy

- Initial improvement in at least three of the clinical signs and symptoms followed by clinically significant worsening in one or more of these clinical findings after 3 to 5 days of therapy

- Development of new pulmonary infection or extrapulmonary infection requiring antimicrobial therapy other than or in addition to the study drug

- Persistence or progression of chest radiographic abnormalities

- Death due to pneumonia

2. Microbiological Outcome

To be considered microbiologically evaluable, patients should meet the criteria outlines for clinically evaluable and should also have a respiratory pathogen identified from culture. Adequate data of various pathogens should be obtained to get approval for a specific organism under this indication.

The microbiologic responses are defined below:

- *Eradication*: The absence of the original pathogens from the post-treatment test-of-cure culture of specimen from the original site of infection

- *Presumed Eradication:* The complete resolution of signs and symptoms is associated with cessation of culturable specimen (e.g., sputum)

- *Persistence*: The presence of the original pathogen in the post-treatment test-of-cure culture specimen from the original site of infection

- *Presumed persistence*: In a patient who is judged to be clinical failure, and a culture of specimen is not possible or is not done, it is presumed that there is persistence of the pathogen

- *Superinfection:* Isolation of a pathogen other than the original pathogen from a specimen taken while the patient is on therapy in a patient who has signs and

symptoms of infection

- *Recurrence*: Isolation of the original pathogens from a culture taken after the test-of-cure visit

- *New Infection:* Isolation of a new pathogen from a post-treatment culture in a patient with signs and symptoms of infection

- *Colonization*: Isolation of an organism from a patient who has no signs or symptoms of infection

H. Statistical Considerations

(Reserved)