Guidance for Industry

Nosocomial Pneumonia — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

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For questions on the content of the draft document contact Renata Albrecht, 301-827-2336.

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GUIDANCE FOR INDUSTRY[1]

Nosocomial 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 nosocomial pneumonia. This guidance document addresses only bacterial nosocomial pneumonia and does not address the study of fungal or viral nosocomial pneumonias.

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 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 nosocomial 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. NOSOCOMIAL PNEUMONIA

A. Regulatory Synonyms

Before the indications of *community-acquired pneumonia* and *nosocomial pneumonia* were identified in the 1992 *Points to Consider* document, patients with these conditions were generally studied under and included in the indication *lower respiratory tract infections*. In more recent years, drugs have been studied and approved using the new names for these indications.

B. Study Considerations

1. Study Characteristics

   If the drug is being studied in community-acquired pneumonia in accordance with the guidance for that indication, an adequate and well-controlled trial should be carried out that establishes safety and effectiveness (i.e., similar or superior effectiveness to an approved product or to a prospectively agreed upon comparator treatment regimen). The Agency should be contacted about the appropriate statistical tests. It is suggested that at least 80 patients would be in each treatment arm. In studies of this infection, patients should meet radiographic and microbiological criteria. Precise case definitions, including specific entry sputum microscopy and radiographic findings, should be included in the trial design.[3] If the drug is being developed only for nosocomial pneumonia, an additional trial establishing safety and effectiveness is recommended.

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

[3] See also Centers for Disease Control and Prevention, "Guidelines for Prevention of Nosocomial Pneumonia," *MMWR* 46: No. RR-1, pp. 1-34, January 3, 1997.

2. Disease Definition

Acute nosocomial pneumonia is broadly defined as pneumonia characterized by a new cough, auscultatory findings consistent with pneumonia, and a new infiltrate or progressive infiltrate(s) on chest radiograph, and accompanied by at least some of the following clinical findings:

- Fever or hypothermia
- Leukocytosis
- Sputum production or a change in the character of the sputum, acquired by a patient in a hospital or long-term-care facility such as a skilled nursing home facility or rehabilitation unit after being admitted for >48 hours
- Present <7 days after a patient is discharged from the hospital with initial hospitalization of ≥3 days duration

In addition, an organism consistent with a respiratory pathogen should be isolated from an appropriately obtained specimen.

Nosocomial bacterial pneumonias are frequently polymicrobial, and enteric Gram-negative bacilli are usually the predominant organisms, including *Klebsiella pneumoniae* and other species, such as *Escherichia coli, Serratia marcescens, Enterobacter aerogenes,* and *Pseudomonas aeruginosa. Staphylococcus aureus* (especially methicillin-resistant strains) and other Gram-positive cocci, including *Streptococcus pneumoniae*, have emerged as important isolates recently. Additionally, *Haemophilus influenzae* is also a pathogen, especially when isolated from mechanically ventilated patients who develop pneumonia within 48 to 96 hours after intubation. Anaerobes account for only 5% of cases. *Legionella pneumophila* and other species have also been reported as the cause of sporadic outbreaks.

Risk factors for nosocomially acquired bacterial pneumonia can be grouped into the following general categories:

- Host factors (e.g., extremes of age and severe underlying conditions, including immunosuppression)
- Factors that enhance colonization on the GI tract by Gram-negative microorganisms (e.g., administration of antimicrobials, ICU admission, chronic pulmonary disease, or coma)

- Conditions favoring aspiration or reflux (e.g., endotracheal intubation, insertion of nasogastric tube, or supine position)

- Conditions requiring prolonged use of mechanical ventilatory support with potential exposure to contaminated respiratory equipment or contact with contaminated or colonized hands of health care personnel;

- Factors that impede adequate pulmonary toilet

C. Inclusion Criteria

The diagnosis of nosocomial bacterial pneumonia should be based on the clinical, radiographic, and microbiologic criteria listed below:

1. Clinical and Radiographic Findings

The patient should have a clinical picture of a new onset of nosocomial bacterial pneumonia $\geq$ 48 hours after hospitalization or admission to a long-term-care facility with a new or evolving infiltrate(s) (not related to another disease process) on chest radiograph, which is not related to another disease process. Fever and leucocytosis should be present. In addition, at least two of the following should be present:

- Cough

- New onset of purulent sputum production or respiratory secretions, 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, tachypnea, or respiratory rate $\geq$ 30/minute, particularly if any or all of these are progressive in nature

- Hypoxemia with a PO_2 <60mm Hg while patient is breathing on room air, as determined by pulse oximetry or arterial blood gas, or respiratory failure requiring mechanical ventilation

The following clinical findings should be met:

- Fever, defined as an oral temperature > 38°C (100.4°F), a tympanic temperature > 38.5°C (101.2°F), or a rectal/core temperature > 39°C (102.2°F) *or* hypothermia, defined as a rectal/core body temperature of < 35°C (95.2°F)

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

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

- 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 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. Microbiologic 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
- endotracheal 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 *Legionella* species, Although an alternative diagnostic test may be used to establish infection with this organism, 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.

Because in evaluation of nosocomial pneumonia there does not seem to be consensus in the literature on the criteria for interpretation of culture results of the specimens obtained from mechanically ventilated patients, the proposed assessment plan for the culture data should be written down and presented to the reviewing division *a priori.*

Two sets of blood cultures (both aerobic and anaerobic) from two different sites should be obtained prior to initiation of the study drug in all patients. Blood cultures taken up to 48 hours prior to initiation of the study drug are acceptable.

Antimicrobial susceptibility testing should be performed on pathogens associated with respiratory tract infections.

D. Exclusion Criteria

(See *General Considerations*)

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

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.

4. Patients with sustained shock, defined as systolic blood pressure <90 mm Hg for >2 hours despite adequate fluid resuscitation, with evidence of hypoperfusion or need for sympathomimetic agents to maintain blood pressure.

5. Patients with APACHE II score <8 or >25.

6. Patients with known or suspected concomitant bacterial infection requiring additional systemic treatment.

7 Patients on immunosuppressive therapy, defined as chronic treatment with known immunosuppressant medications (including chronic treatment with >10 mg/day of systemic prednisone or equivalent).

8. Patients with neutropenia, defined as an absolute neutrophil count <1000/mm.

9. Patients with history of any form of epilepsy or seizure.

10. Patients with evidence of recent alcohol or drug abuse or dependence.

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 ≥80% compliance for an assessment of a favorable clinical outcome. Depending on the antimicrobial agent, the proposed duration of therapy may vary; however, the specific dose regimen and duration should be clearly stated in the protocol.

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)
- 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

Daily clinical assessments should be recorded in the case report form. The laboratory assessments to be made during the course of the study can be individualized somewhat for the antimicrobial agent causative respiratory pathogen. However, some general principles follow:

- 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 serum chemistry 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 that of 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

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.

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.

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

Patients should meet the clinical criteria outlined above and should also have a respiratory pathogen identified from culture.

As noted above, there is a lack of consensus on how to evaluate culture results from patients who are on mechanical ventilation and have a diagnosis of nosocomial pneumonia. These patients should be evaluated separately from other patients with this diagnosis.

The microbiologic responses are defined below:

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

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

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

d. *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

e. *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

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

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

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

H. Statistical Considerations

(Reserved)