

Guidance for Industry

Acute Bacterial Exacerbation of Chronic Bronchitis — Developing Antimicrobial Drugs for Treatment

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GUIDANCE FOR INDUSTRY¹

Acute Bacterial Exacerbation of Chronic Bronchitis — Developing Antimicrobials 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 antimicrobials for the treatment of acute bacterial exacerbation of chronic bronchitis.

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 one location. Where appropriate, this guidance contains relevant information from several

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 antimicrobials for the treatment of acute bacterial exacerbation of chronic bronchitis. 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.

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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. ACUTE BACTERIAL EXACERBATION OF CHRONIC BRONCHITIS

A. Regulatory Synonyms

Some common synonyms include:

The term *lower respiratory tract infection*, has been used in the past to describe infections of the respiratory tract, which could encompass *bronchitis* as well as *pneumonia*. More recently, the *Points to Consider* document recognized four subcategories for infections of the lower respiratory tract, including two for bronchitis: *acute exacerbation of chronic bronchitis* (AECB) and *secondary bacterial infection of acute bronchitis* (SBIAB). The IDSA guidance includes the diagnostic category AECB, but not SBIAB.

It has been increasingly recognized that the etiology of acute bronchitis is predominantly nonbacterial. Most cases of acute bronchitis are viral or noninfectious. Although secondary invasion by such bacterial pathogens as *Streptococcus pneumoniae* or *Haemophilus influenzae* may occur, there has not been definitive demonstration of this chain of events or of its frequency. Therefore, the discussion of this indication will address only *acute exacerbation of chronic bronchitis* (AECB).

B. Study Considerations

1. Study Characteristics

A statistically adequate and well-controlled trial is recommended establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product). In this trial, an evaluable patient should be both clinically and microbiologically (any putative pathogen) evaluable. Analysis of the data should confirm the general correlation between

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

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clinical improvement and bacterial eradication (or suppression) in the evaluable patients.

If the product is not being developed for pneumonia, a second study is suggested, in which clinical effectiveness is the primary effectiveness endpoint. Although microbiologic studies should be performed on each patient, pathogen isolation at baseline or susceptibility to either trial drug should not be required for overall evaluability. Patients in this trial should be analyzed in two separate groups: (1) those who were clinically evaluable (whether or not microbiologically evaluable) and (2) the subset of patients who were clinically evaluable and microbiologically evaluable. The trial should employ rigorous entry and evaluability criteria to ensure the likelihood of bacteria being responsible for the exacerbation. Analyses of data should confirm (by means of comparing the direction of the independent 95% confidence interval testing) the successful outcome rates established for the overall clinically evaluable and for the clinically and microbiologically evaluable subset of patients. Likewise, the analyses should establish the general correlation between clinical improvement and bacterial eradication (or suppression) in the clinically and microbiologically evaluable subset of patients.

If effectiveness in either community acquired pneumonia or nosocomial pneumonia is established by the product at the same dosing regimen (dose and duration) for the three clinically relevant (AECB) microorganisms, the one *clinically plus microbiologically evaluable study* (see paragraph 1 above) should be sufficient to establish the effectiveness of the antimicrobial drug product in the treatment of this infection.

If acceptable clinical and microbiologic responses are shown for *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*, approval of these three microorganisms should currently be given in this indication. As evidence accumulates that other microorganisms are pathogenic AECB, consideration should be given to their addition to the list of approved pathogens.

2. Disease Definition

A discussion of the spectrum of AECB (summarized from major textbooks on adult and pediatric infectious diseases) is given below.

Bronchitis is an inflammatory condition of the tracheobronchial tree. Chronic bronchitis is usually defined as a condition characterized by cough and sputum production on most days during 3 consecutive months for >2 successive years. The underlying problem is typically exposure to bronchial irritants, most commonly cigarette smoke, with resulting obstructive pulmonary disease and emphysema. Acute exacerbation of this chronic process is characterized by increased cough, sputum production, and dyspnea, in addition to development of sputum purulence. These symptoms may be due to viral infection in

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25-50% of patients. The role of bacterial infection in exacerbation of chronic bronchitis is unclear since patients may have *S. pneumoniae*, *H. influenzae*, or *Moraxella catarrhalis* isolated from sputum cultures between episodes of acute illness. *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* generally are accepted as the most frequent bacterial causes of acute exacerbation of chronic bronchitis. Less common isolates are *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. While the role of bacteria in the pathogenesis of the acute process and the role of antimicrobial agents in the management of the acute process continue to be investigated, evidence exists that antimicrobials have clinical benefit. Some patients who show complete clinical response may continue to harbor the pathogen as a colonizer in the respiratory secretions (making outcome assessment problematic). Chronic bronchitis is poorly defined in pediatric patients and usually overlaps with asthmatic bronchitis, in that both are characterized by persistent cough and wheezing. An infectious etiology may be postulated.

C. Inclusion Criteria

Patients enrolled in clinical studies of AECB should be adults with a well-documented history of chronic bronchitis. To be clinically eligible for this indication, patients should have a clinical diagnosis of AECB based on history, physical examination and radiographic examination.

1. Patients should have a history of chronic bronchitis, characterized by cough and sputum production on most days for 3 consecutive months for >2 successive years. The acute process should be characterized by increased cough, sputum production and dyspnea. Fever may be present. Documentation of both the chronic process and the acute exacerbation can be made on the basis of the history and physical examination. Pulmonary function studies (FVC, FEV₁, TLC, peak flow, ABGs, FVC (forced vital capacity), FEV (forced expiratory volume), TLC (total lung capacity), WBC (white blood cells), ABG (arterial blood gases)) may be used to document pulmonary dysfunction accompanying AECB, as well as to document the presence and severity of underlying chronic obstructive pulmonary disease.
2. Physical examination should be performed, and any abnormal findings documented, especially those pertinent to the respiratory tract. The presence of purulent sputum, defined as > 25 WBC per field and < 10 squamous epithelial cells at 100x magnification (low power, 10x objective), should be documented.
3. Radiographic documentation should include a chest x-ray, which serves to exclude pneumonia.

Patients should have a *microbiological* diagnosis of AECB based on isolation of a pathogen from a sputum sample. For adequate evaluation, it is important that the patient receive proper

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instruction on providing a sputum and not a saliva sample and that the clinical laboratory evaluate the adequacy of the specimen.

Documentation should include Gram's stain examination of the specimen, quantitation of WBCs and oral epithelial cells, and isolation of a pathogen on culture and results of susceptibility testing. The sputum specimen is considered to be adequate when it contains < 10 squamous epithelial cells and > 25 WBC per field at 100x magnification (low power, 10x objective).

D. Exclusion Criteria

Patients with cystic fibrosis, tuberculosis, bronchiectasis, or pulmonary malignancies should be excluded. If patients receiving systemic steroids in a dose of ≥ 10 mg per day of prednisone (or the equivalent) are included, the study patients should be stratified according to the use of concomitant steroid therapy.

E. Drugs and Dosing Regimen

Adequacy of therapy is defined as a patient who has received $\geq 80\%$ (or within 80-120%) of the prescribed dose amount and/or dosing regimen. Dosing should be documented as should compliance (diary or urine test for latter). Patients who received at least 72 hours of therapy and are not doing well should be classified as failures.

Test Drug: Lot number and other identifier should be provided (safety recommendation).

Control Drug: While any drug and dosing regimen approved by the FDA may be used, consideration should be given to a regimen considered clinically relevant in the geographic area where the study was conducted. For example, a beta-lactamase stable drug should be used in areas with a high incidence of beta-lactamase producing organisms. A minimum target efficacy rate for that drug should be provided.

F. Evaluation

1. Entry/Pre-Therapy Visit

To be evaluable, the patients should have an entry visit. The following information from the initial visit should be included in the patient record: date of visit, clinical signs and symptoms of present episode of bronchitis, including a qualitative and quantitative description of the sputum, duration of current symptoms, past history of chronic bronchitis, history of cigarette smoking, use of concurrent medications such as steroids and/or bronchodilators, results of the clinical examination, radiologic examination (chest

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x-ray), sputum characterization and culture results, and laboratory test results. Hospital status (inpatient vs outpatient) should be documented.

The following pre-exacerbation patient information should also be recorded: cough frequency, sputum volume and characteristics, baseline supplemental oxygen use, recent history of antibiotic use, and history of allergies.

2. On-Therapy Visit

During the first week, the patient should have an on-therapy assessment either in the investigator's office or by phone. If the patient is doing well, therapy is continued. If the patient is considered to be failing therapy, the drug is stopped and the patient is prescribed another antimicrobial; a sputum Gram's stain and culture should be obtained. If the patient is seen for the on-therapy visit, findings from this visit (e.g., history, physical examination, laboratory test results) should be documented in the patient record. If the patient is contacted by telephone, documentation of specific questions asked and responses given should be included in the record. This visit is strongly recommended for good study conduct.

Note: The IDSA guidance recommends a 3- to 5-day visit and weekly examinations thereafter until end of therapy, then clinical and microbiological assessment at 48 hours, 7 to 14 days and 21 to 28 days after the completion of therapy

3. End-of-Therapy Visit

This visit is optional. If clinical examination and other tests are performed at this visit, they may be included in the case record. However, this visit should not be considered a test of cure visit.

4. Post-Therapy (Test-of-Cure) Visit

This visit should occur approximately 1 to 2 weeks after the completion of therapy. The results of the clinical evaluation, including status of all presenting signs and symptoms as well as emergence of any new signs and symptoms of bronchitis or pneumonia should be documented. Radiographic examination is not necessary unless clinically indicated. The character of the sputum and results of repeat Gram's stain and culture should be documented.

No additional visits are routinely necessary.

G. Outcome

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1. Clinical Outcome

Clinical response is the primary determinant of efficacy for the indication of bronchitis.

a. Clinical Cure

Patient meets entry criteria and resolution of the acute signs and symptoms at the test-of-cure visit. For patients with chronic bronchitis, this should be interpreted as return to baseline condition (see IDSA guidelines, page S79). No antibiotics (other than per protocol) should have been given. The category of clinical improvement should be avoided for purposes of drug development. If it is unclear whether the patient meets either the cure or failure category, further follow-up should be planned. If the improved symptoms persist and additional antimicrobials are added, then the patient is *failure*. If the patient returns to baseline condition without additional antimicrobial therapy, the patient should be classified as a cure.

b. Clinical Failure

Patient should be considered a failure if there is persistence or worsening in the signs or symptoms of the acute process, or need for hospitalization (rehospitalization). Also, patients who receive additional antimicrobials or whose antimicrobial therapy is changed should be considered failures. If a patient is classified as a failure at the on-therapy or end-of-therapy visit, this evaluation of failure should be carried forward into the final visit outcome. That is, for the purpose of calculating outcome rates -- once a failure, always a failure.

Note: No distinction is thus made between failure and relapse.

2. Microbiological Outcome

A microbiological evaluation is not appropriate if a baseline pathogen is not identified.

a. Presumed Eradication

In the absence of a repeat sputum culture, a patient should be considered a presumed eradication if the definition of clinical cure is met.

b. Eradication

The absence of the entry pathogen from a repeat sputum culture performed 1 to 2 weeks post-therapy in a patient with chronic bronchitis.

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c. Presumed Persistence

In a patient who is classified as a clinical failure, as defined above, it should be presumed that there is persistence of the original pathogen.

d. Persistence

Presence of the original pathogen on repeat culture of the sputum done on therapy or at the 2 to 4 weeks (1-2 weeks) post-therapy evaluation.

e. Superinfection

Isolation of a new pathogen on therapy in a symptomatic patient.

H. Statistical Considerations

The primary endpoint for evaluation is clinical outcome. Analyses of the intent-to-treat population should also be performed. However, patients should meet the clinical criteria of having increased sputum production, cough, other symptoms referable to the tracheobronchial tree and a sputum Gram's stain that is consistent with a bacterial infectious process to be considered evaluable. Eradication rates of individual pathogens in patients who have the causative organisms isolated at baseline should also be tabulated.