Guidance for Industry

Acute Bacterial Sinusitis — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

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Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573, or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

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GUIDANCE FOR INDUSTRY[1]

Acute Bacterial Sinusitis — 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 sinusitis.

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 antimicrobials for the treatment of acute bacterial sinusitis. 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. ACUTE BACTERIAL SINUSITIS

A. Regulatory Synonyms

Acute sinusitis is an infection of one or more of the paranasal sinuses. Synonyms include *acute maxillary sinusitis, acute bacterial sinusitis,* and *acute community-acquired sinusitis*. In early approvals, this condition may have been included under *upper respiratory tract infections* or *infections of the ear, nose and throat*.

> *Note*: Ethmoid and maxillary sinuses are present at birth; sphenoid and frontal sinuses develop by 6 years of age, but change over time. FDA considers postpubertal patients to have the same disease condition as adults.

This guidance document does not presently address the indication of chronic sinusitis. The clinical presentation, microbiologic etiology, and treatment of patients with chronic sinusitis differ from that of patients with acute sinusitis. As noted in the IDSA guidance, the role of antibiotic therapy in the treatment of chronic sinusitis is less well defined than in acute sinusitis, and placebo-controlled trials may be justified for this indication.

B. Study Considerations

A statistically adequate and well-controlled multicenter trial is recommended establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product). In this trial, rigorous case definitions should be used with specific clinical and either computer tomographic, radiographic, or ultrasonic entry criteria and endpoints as the primary effectiveness parameters. Sinus puncture need not be performed in this study, although sinus punctures of patients judged to be therapeutic failures should be strongly encouraged to document any bacterial pathogens not

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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.*

adequately treated in the trial.

In addition, another a trial should be conducted, in which successful microbial, clinical, computer tomographic, radiographic, or ultrasonic outcome is established in at least 100 patients. This study should establish an acceptable microbial and clinical outcome in at least 25 patients with *Haemophilus influenzae*, in at least 25 patients with *Streptococcus pneumoniae*, and in at least 15 patients with *Moraxella catarrhalis*. To establish the efficacy of an antimicrobial in the treatment of patients with acute sinusitis due to *Staphylococcus aureus*, approximately 10 to 20 patients with this isolate should be evaluated, adhering to the specific criteria presented in the microbiology section of this document. Post-therapy sinus puncture is strongly encouraged in those patients judged to be therapeutic failures so that bacterial persistence or superinfection can be determined. In this trial, outcomes on all patients enrolled should be reported, not just those patients with the bacterial pathogens mentioned previously in this paragraph. This trial should be performed by at least two investigators in geographically diverse regions, and no one center should contribute more than 55% of the evaluable patients.

If a product failed to eradicate the major bacterial pathogens associated with this infection, the product should receive a *restricte*d listing as "not a product for first line therapy." This restriction should be based on the empirical nature of the treatment of this disease at the present time and the need for true first-line therapies to be efficacious against the major bacterial pathogens associated with this infection.

C. Inclusion Criteria

Male and female patients of any age can be enrolled; adult patients should be studied separately from pediatric patients.

Patients should have a *clinical* diagnosis of acute sinusitis based on history, physical examination, and radiographic examination. It is assumed that in most patients this means acute maxillary sinusitis, although involvement of other sinuses will often be present.

For the diagnosis of acute sinusitis, a history of signs and symptoms lasting for longer than 7 days, but less than 28 days should be solicited. These should include facial pain, pressure, and tightness, typically over the maxillary sinuses and periorbital region; a purulent anterior or posterior nasal discharge; nasal congestion; and cough. Other complaints may be headache, fever, bad breath, change in perception of smell, toothache, tearing, and periorbital swelling. In children, otitis media may be present concurrently.

Patients with a history of allergic rhinitis should be identified upon entry into the study so that they may be analyzed separately. Underlying nasal mucosal inflammation in allergic rhinitis patients may result in different clinical outcomes from nonallergic patients, and it may be difficult

to distinguish between signs and symptoms due to allergy versus infection (mucosa edema, congestion, rhinorrhea).

Physical examination findings should be recorded. This examination should document clinical evidence of paranasal sinus involvement, such as tenderness or pain upon percussion of the sinuses and the presence of a purulent nasal or post nasal discharge. The examination may also demonstrate discharge originating from the sinus, inflamed and swollen nasal mucosa, and fever.

Radiographic documentation should include CT scan, standard sinus x-rays (e.g., basal, Caldwell, lateral, and Water's projections), or ultrasound examination of the affected sinuses, and should comment about sinus abnormalities such as mucosal thickening, air-fluid levels, or sinus opacity. Of these modalities, CT scan is the preferred imaging technique when available.

The microbiological diagnosis of acute sinusitis is based on isolating a bacterial pathogen from a specimen obtained by maxillary sinus puncture at baseline. Early reports suggest the potential value of endoscopically guided cultures of the middle meatus in predicting the microbial etiology of acute maxillary sinusitis. However, endoscopically guided cultures are not a currently acceptable means of establishing microbiological diagnosis because they may be contaminated by nasal cavity flora (particularly staphylococcal species). Further studies are required to define the role of this procedure in clinical trials.

Documentation should include Gram's stain examination with WBC and bacterial morphotype semiquantitation, quantitative bacterial cultures, and antimicrobial susceptibility testing. The pathogens should be susceptible to the study and control drugs. However, should the patient show clinical improvement, despite the isolation of a non-susceptible organism by in vitro testing, the investigator may elect to continue treatment with the study drug and to collect all protocol-specified data.

Isolation of the common pathogens *Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis* from a maxillary sinus puncture aspirate is considered significant independent of colony count data. *Staphylococcus aureus* is considered a pathogen (an etiological agent) when isolated in pure culture with bacterial counts $\geq 10^4$ CFU/ml.

In the 1990s, the three most common bacterial pathogens are *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis.* Some reports state that *Streptococcus pneumonaie* and *Haemophilus influenzae* comprise 50% of the bacterial pathogens in adults, while *Moraxella catarrhalis, Streptococcus pneumonaie* and *Haemophilus influenzae* comprise two-thirds of the bacterial pathogens in children. As stated above, 25, 25, and 15 evaluable isolates, respectively, should be available for an assessment of outcome in this disease. Other infrequently isolated pathogens are *Streptococcus pyogenes, Staphylococcus aureus* and *Pseudomonas aeruginosa.* Anaerobes are seen in a small percentage of cases, usually ones

associated with dental disease.

D. Exclusion Criteria

(See also *General Considerations.*)

Patients with a history of chronic sinusitis, as defined in the IDSA guidance, should be excluded from enrollment since their baseline symptomology and examination findings may confound the assessment of study drug efficacy.

E. Drugs and Dosing Regimen

To be evaluable, the patient should receive within 80-120% of the prescribed dose amount and/or dosing regimen. Dosing should be documented, as should compliance (diary or urine test for the latter). If a patient received 72 hours of therapy and is not doing well, the patient may be classified as a failure.

Test Drug: Lot number and other identifier should be provided (safety, not evaluability 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 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 organism. A minimum target efficacy rate for that drug should be provided.

F. Evaluation

1. Entry Visit

The following information from the initial visit should be included in the final case report form: date of visit; clinical signs and symptoms of present episode of sinusitis; relevant past history of sinusitis episodes or respiratory allergies (including baseline allergy-related symptomology during the two week period prior to onset of sinusitis symptoms); results of the clinical examination including ears, nose, throat and teeth; radiologic examination (CT, x-ray or ultrasound); quantitative sinus puncture culture and antimicrobial susceptibility testing (if done); and laboratory test results.

2. On-Therapy Visit

In clinical practice, physicians see patients approximately 3 to 5 days into therapy to

evaluate the patient's response to therapy. 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. 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, but its absence should not serve as the only reason for exclusion from evaluability.

Note: IDSA recommends a 2- to 3-day and 5- to 7-day on-treatment visit, then weekly or biweekly until resolution of symptoms. A repeat sinus puncture is also recommended for microbiological assessment in all clinical nonresponders at 72 hours.

3. End-of-Therapy Visit

In clinical practice, physicians may see patients near the completion of therapy to optimize patient care. 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 sinusitis, should be documented. Results of radiographic examination should be documented and employ the same modality used to diagnose the infection (i.e., CT, sinus x-rays, or ultrasound). If a sinus puncture is performed, the results of the culture and antimicrobial susceptibility testing should be documented.

5. Late Post-Therapy Visit

Additional visits are not necessary, except for patients who are not seen at the test-of-cure visit or who have a response of failure at the test-of-cure visit.

G. Outcome

1. Clinical Outcome

a. Clinical Cure

Patient meets above evaluability criteria and has resolution of signs and symptoms at the test-of-cure visit, and at least no worsening in the radiographic appearance of the sinuses. No antibiotics (other than per protocol) were given.

b. Clinical Failure

Patient is considered a failure if there is persistence of one or more signs or symptoms of sinusitis (including the appearance of the new ones). Also, patients who receive additional antimicrobials or whose antimicrobial therapy is changed are 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.

c. Unknown

Patient not seen for test-of-cure visit or clinical outcome not recorded at the test-of-cure visit. These patients would be considered unevaluable for a clinical outcome, but would be counted in the intent-to-treat evaluation.

2. Microbiological Outcome

The specimen for microbial evaluation for this disease should be obtained through a direct sinus puncture. It is recognized that patients may elect not to undergo this procedure at follow-up visits; therefore, the microbiologic outcome may be presumed, based on clinical findings, as defined below. A microbiological evaluation is not possible if a baseline pathogen is not identified.

a. Presumed Eradication

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

b. Documented Eradication

The absence of the entry pathogen from a repeat sinus puncture at 1 to 2 weeks post-therapy.

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 of culture in a sinus puncture taken 1 to 2 weeks post therapy.

H. Statistical Considerations

(Reserved)