

Draft - Not for Implementation

Guidance for Industry

Acute Otitis Media — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573,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>.

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

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
July 1998
Clin-Anti**

Draft - Not for Implementation

TABLE OF CONTENTS

I. INTRODUCTION 1

II. BACKGROUND 1

III. ACUTE OTITIS MEDIA 2

A. Regulatory Synonyms 2

B. Study Considerations 2

C. Inclusion Criteria 4

D. Exclusion Criteria 5

E. Drugs and Dosing Regimens 6

F. Evaluation 6

G. Outcome 8

H. Statistical Considerations 11

GUIDANCE FOR INDUSTRY¹

Acute Otitis Media — 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 antimicrobials for the treatment of acute otitis media.

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

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 Immunologic 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 antibacterial drug products for the treatment of acute otitis media. 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.

Draft - Not for Implementation

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 OTITIS MEDIA

A. Regulatory Synonyms

A number of synonyms are used to discuss this indication, including *acute bacterial otitis media*, *acute suppurative otitis media*, *acute purulent otitis media*, and *otitis media*. Acute otitis media has been mistakenly referred to as *otitis media with effusion*; the latter should be reserved for patients who are asymptomatic and have an isolated middle ear effusion (MEE) identified by pneumatic otoscopy.

Acute otitis media is an inflammation of the middle ear, manifested by localized signs or symptoms, such as ear pain, hearing loss, and accompanied by nonspecific symptoms such as, fever, irritability, inconsolability, nausea, and vomiting.

Recurrent otitis media is ≥ 3 distinct and well-documented episodes in the previous 6 months or ≥ 4 in 12 months.

B. Study Considerations

1. Study Characteristics

A statistically adequate and well-controlled multi-center trial is recommended establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product). In this trial, rigid case definitions should be used with specific subjective and objective

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

Draft - Not for Implementation

diagnostic and effectiveness parameters clearly defined. This trial ordinarily should not enroll children less than 6 months old. Baseline tympanocentesis need not be performed in this study; however, tympanocentesis of patients judged to be therapeutic failures is strongly encouraged to document potential specific bacterial pathogens not adequately treated in the trial.

In addition, another trial should be conducted using tympanocentesis or other validated detection methodology at baseline to establish microbiologic etiology. This study should establish acceptable microbial and clinical outcome in at least 25 patients with *H. influenzae*, in at least 25 patients with *S. pneumoniae*, and in at least 15 patients with *M. catarrhalis*. Post-therapy tympanocentesis is encouraged in those patients judged to be therapeutic failures so that bacterial persistence or superinfection could be determined. In this trial, outcomes on all patients enrolled should be reported, not just on 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. As etiologic patterns change, the requisite microorganisms listed would also change. With the increasing incidence of penicillin-resistant streptococcus pneumoniae, additional clinical and in vitro data may be necessary before this pathogen may be included in approved labeling. The Agency should be contacted for the latest guidance.

Pathogens listed in the final product label should be those (of the three listed above) that had acceptable eradication rates. If a product fails to have acceptable clinical and microbiologic effectiveness against all three microorganisms, the product should be listed only for those microorganisms that it has eradicated. The product should also receive a *restricted* listing as *not a product for first line therapy*. This restriction should be based on the empiric nature of the treatment of this disease at the present time and the need for first-line therapies to be effective against all of the presently common bacterial pathogens associated with this infection. To receive an unrestricted label in this infection, the investigative product should be compared to a product with an unrestricted label in the *clinical only trial* defined in the following section.

Because of the invasiveness of a tympanocentesis, the *Points-to-Consider* document distinguished between studies in which patients are clinically evaluable (clinical-only study), and those who are both clinically and microbiologically evaluable. *Clinical-only* studies are those where the signs, symptoms, and tympanometry or electroacoustic reflectometry results are consistent with acute otitis media. Clinical/microbiological studies are those where the signs, symptoms, tympanometry or electroacoustic reflectometry results, and tympanocentesis sampling (culture results) are consistent with

Draft - Not for Implementation

acute otitis media.

2. Resistance and *Streptococcus pneumoniae*

S. pneumoniae resistance has become an increasing concern for the global medical community. *S. pneumoniae* is the major pathogen in acute otitis media. Because of this concern, 25 patients with *S. pneumoniae* may be insufficient to garner approval for this pathogen in acute otitis media. Greater certainty in the investigational drug's purported efficacy against this pathogen may be desirable.

C. Inclusion Criteria

Male and female pediatric patients usually are enrolled. Adult patients are enrolled infrequently. To be clinically evaluable at entry, patients should have a *clinical* diagnosis of otitis media based on history, physical examination, pneumatic otoscopy, and tympanometry or electroacoustic reflectometry.

Rigorous documentation of signs and symptoms is of particular importance in the clinical-only study. In the clinical-only study, microbiologic diagnosis is not available to distinguish patients with acute otitis media due to bacterial etiology from those with simple hyperemia, viral otitis media, or otitis media with effusion.

1. Signs and Symptoms

Signs or symptoms that may be present in patients with acute otitis media and may help confirm the diagnosis include one or more of the following:

- Ear pain or ear ache
- Ear fullness
- Discharge from external canal (following *acute* perforation of the tympanic membrane)
- Decreased hearing

Additional generalized signs and symptoms that are consistent with a diagnosis of acute otitis media (but are otherwise nonspecific) include:

- Fever
- Vomiting

Draft - Not for Implementation

- Diarrhea
- Fussiness or irritability
- Inconsolability
- Anorexia or refusal to eat
- Sleep disturbance

Infants and younger children often present with nonlocalizing symptoms. Older children are more likely to articulate symptoms referable to the ear.

2. Pneumatic otoscopy

The otoscopic findings considered most consistent with acute bacterial otitis media and that should be documented at entry on the case report form include:

- a. Bulging tympanic membrane, which may be erythematous

Note: Because hyperemia may be present in a febrile or crying child, a red tympanic membrane alone is inadequate for the diagnosis of acute otitis media.

- b. Loss of the normal light reflex and tympanic membrane landmarks
- c. Abnormal tympanic membrane mobility on biphasic pneumatic otoscopy due to the presence of pus or fluid behind the membrane and edema of the membrane

3. Tympanometry

Entry tympanometry and/or electroacoustic reflectometry should be obtained on all children at baseline. If tympanometry is used, acceptable results for inclusion include either *type B* or *positive pressure peak* curves (unless the tympanic membrane is perforated at entry).

D. Exclusion Criteria

Patients with the following conditions should not be enrolled:

- Tympanostomy tubes present
- Otitis externa
- Systemic anti-infective drug product in the previous 7 days prior to enrollment

Draft - Not for Implementation

- (clinical-only study)
- Systemic anti-infective drug product in the previous 3 days prior to enrollment (clinical/microbiological study)
- Patient receiving antimicrobial prophylaxis for recurrent otitis media

Perforated tympanic membranes need not be excluded.

Note: However, for the clinical/microbiological study, if perforation is present for >48 hours at the time of sampling, the patient should be excluded. Patients with a history of recurrent otitis media need not be excluded, but should be enrolled with planned subset analyses.

E. Drugs and Dosing Regimens

The patient should receive at least the first 3 consecutive days of the prescribed dosing regimen to be evaluable. Dosing should be documented, as should compliance (diary and/or urine test).

Control Drug: Although any drug and dosing regimen approved by the FDA may be potentially used as a comparator, consideration should be given to a regimen considered clinically relevant in the patient population to be studied.

F. Evaluation

1. Entry Visit

Clinical-only Study: At entry, the patient should have received an appropriate history and physical examination. The following information should be recorded on the case report form during the entry examination:

- Date of visit
- Signs and symptoms
- Unilateral or bilateral acute otitis media (identify affected ears)
- Number of distinct and well-documented episodes of acute otitis media in the previous 12 months
- Otoscopic findings for each ear (including pneumatic otoscopy)
- Overall severity of disease (mild, moderate, severe)
- Tympanometry and/or electroacoustic reflectometry for each affected ear
- Absence or presence of tympanic membrane perforation for each ear
- Other laboratory tests.

Draft - Not for Implementation

- Thickening of the tympanic membrane, indicating a chronic process

Clinical/Microbiological Study: In addition to the information outlined for the clinical-only study, for the clinical/microbiological study, the entry visit should include a baseline tympanocentesis (where done in the clinical/microbiological study) and submission of middle ear fluid for culture and susceptibility testing. However, if perforation of the tympanic membrane is present at study entry, sampling of the exudate is acceptable so long as the sample was obtained within 48 hours from the time of perforation.

For microbiological assessment, the following information should be collected:

- Identification of the affected ears sampled (right and/or left).

Note: If bilateral otitis media is present, both ears should be sampled.

- A description of how the sample was obtained (tympanocentesis or swab of exudate – where perforation exists)
 - Speciation of the bacterial isolate
 - In-vitro susceptibility testing, for both the study and control drugs, of the isolates
2. On-Therapy Visit (Timing of visit: 3 to 5 days into therapy)

For the purposes of good study conduct, the on-therapy visit is strongly recommended, but its absence should not cause a patient to be considered nonevaluable at the test-of-cure visit. If the patient is responding favorably to therapy, the clinical management is typically left unchanged. If the patient is not responding to therapy, the patient is frequently switched to another antimicrobial agent.

In the clinical/microbiological study, assuming the baseline pathogen is found to be resistant to either study drug, the patient need not be withdrawn from the study as long as the patient is clinically responding to the study drug. Patients who are not responding to therapy (in either the clinical or clinical/microbiological study) should undergo tympanocentesis; the sample should be sent for culture and susceptibility testing; and the subject should be changed to another anti-infective therapy.

3. End-of-Treatment Visit (Optional)

Draft - Not for Implementation

This visit provides little overall clinical value to assessing a drug's efficacy in the treatment of acute otitis media, unless the patient is failing. However, sponsors may opt to include this visit to assess the safety of the drug (i.e., monitor laboratory changes).

4. Test-of-Cure (TOC) Visit (Timing of visit: 2 to 4 weeks after study entry)

The results of the clinical evaluation of acute otitis media, including status of all presenting signs and symptoms as well as emergence of any new signs and symptoms should be recorded.

The investigator should answer the following question on the case report form:

*In your opinion, does the patient require additional systemic anti-infective treatment for this episode of acute otitis media? (yes/no) If yes, please explain why.*_____

5. Late Post Treatment Follow-up (Optional)

G. Outcome

The clinical response in acute otitis media should address the entire patient, not be limited solely to the affected ear at study entry. For example, if a patient is enrolled with right otitis media and subsequently during therapy develops left otitis media (with resolution of the right ear infection), the patient's response should not be considered *clinical cure* with a new infection. Rather, the patient's overall response should be clinical failure.

1. Clinical (applicable to both clinical-only and clinical/microbiological studies)

a. *Clinical Cure* (only valid at the test-of-cure visit): Patient experiences resolution of signs and symptoms at TOC visit. This response should be objectively defined in the protocol. No additional systemic anti-infective drugs (other than specified per protocol) were given to the patient during the study period.

Note: Persistent middle ear effusion (MEE) at the TOC visit should be noted on the case report form, but should not be taken into account when determining clinical outcome.

Draft - Not for Implementation

b. *Clinical Failure* (valid following ≥ 72 hours of study drug): The patient is considered a clinical failure if there is lack of improvement or worsening of the patient's signs and/or symptoms at any point following ≥ 72 hours of study drug.

Patients who receive additional systemic anti-infective drugs any time between entry and the test-of-cure visit are considered clinical failure *unless* this therapy was initiated for a reason unrelated to the initial infection. In this case, the patient should be considered nonevaluable. If a patient is deemed a clinical failure as early as day 3 of the study, this clinical response should be carried forward to the test-of-cure visit.

2. Microbiological Responses (applicable to clinical/microbiological study only)

The three most common bacterial pathogens for acute bacterial otitis media are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Other less frequently isolated pathogens include *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. For purposes of evaluability and outcome assessment, if a patient has the same pathogen isolated from both ears, that patient is considered to have a single pathogen and it should only be counted once (e.g., *S. pneumoniae* isolated from both left and the right MEEs). Conversely, if a patient has a pathogen isolated from one MEE and a different pathogen isolated from the contralateral ear, both pathogens may be counted in the microbiological outcome assessment.

a. *Presumed Eradication* (only valid at the TOC visit): For most patients, it is anticipated that microbiological eradication will be determined based on an adequate clinical response to therapy at the TOC visit (i.e., there is no need to resample the ear in a patient who is clinically well).

b. *Documented Eradication* (only valid at the TOC visit): Repeat tympanocentesis of MEE at the TOC visit is sterile. Tympanocentesis obtained only at the on-therapy visit should not be considered evidence of documented eradication. Rather, a negative culture result may represent antimicrobial suppression.

c. *Documented Persistence* (valid at any time point following ≥ 72 hours of study drug): The original pathogen is isolated from a culture obtained by repeat tympanocentesis.

Draft - Not for Implementation

d. *Presumed Persistence* (valid at any time point following ≥ 72 hours of study drug): A patient who is deemed to be a clinical failure by the investigator (or who receives additional systemic anti-infective therapy prior to the test-of-cure visit for acute otitis media) is presumed to have persistence of the baseline pathogen.

e. *Superinfection* (valid from day 3 of study onwards): Isolation of a new pathogen (isolated by tympanocentesis) during the study period (day 3 onwards)

3. Microbiologic Efficacy Caveats

- For the purposes of outcome analysis, if a patient has a pathogen isolated from one ear at entry, and that same pathogen is isolated **only** from the contralateral ear at follow up, the microbiological response should be considered documented persistence.
- If the tympanic membrane is perforated at study entry, a sample of the exudate should be sent for culture and susceptibility testing, as long as this sample was obtained within 48 hours of the perforation. Only *Streptococcus pneumoniae*, *Haemophilus influenzae*, and/or *Moraxella catarrhalis* isolated using this sampling technique are considered interpretable. If the sample is obtained >48 hours of the perforation, the microbiologic results should be considered uninterpretable.
- The division recommends that tympanocentesis be performed in any patient who is judged to be failing therapy (in either the clinical-only or the clinical/microbiological study). The obtained sample should be cultured and susceptibility testing for each isolate should be performed. However, absence of a follow-up culture should not be considered a reason for deeming a patient non-evaluative because bacteriological responses can be presumptively derived.

4. Intent to Treat (ITT) (applicable to both clinical-only and clinical/microbiological studies)

The ITT population is defined as any subjects meeting the entry study characteristics. (See *General Considerations* document, section XX, Statistical Considerations.) The ITT population will differ for the clinical-only and clinical/microbiological studies. For the clinical-only study, the ITT population should represent patients who meet the study inclusion and exclusion criteria. For

Draft - Not for Implementation

the clinical/microbiological study, in addition to what is expected of the clinical-only study, the ITT population should have undergone tympanocentesis in one or both ears at study entry.

5. Entry Criteria Summarized

a. Clinical-Only Study

- Well-documented signs and symptoms of acute otitis media at study entry
- Bulging tympanic membrane on otoscopy at study entry
- Biphasic pneumatic otoscopy consistent with a MEE at study entry
- Tympanometry or electroacoustic reflectometry consistent with MEE at study entry. If tympanometry is used, either type B or *positive pressure peak* curves are considered evaluable (unless the tympanic membrane is perforated at entry).
- At least the first 3 consecutive days of the prescribed dosing regimen
- No concurrent systemic anti-infective drug use during the study period
- Assessable at the TOC visit (failures are assessable as early as day 3 of study and their responses are carried forward to the TOC visit)
- No systemic anti-infective therapy within 7 days of study entry

Note: The on-therapy visit is strongly encouraged, but, if not done, will not affect evaluability.

b. Clinical/Microbiological Study (same as *Clinical-only Study* above including)

- No systemic anti-infective therapy within 3 days of study entry (note difference from clinical-only study)
- Isolation of a baseline pathogen via tympanocentesis using appropriate sterile technique
- Isolation of a baseline pathogen via culture of exudate from a perforated tympanic membrane at study entry (within 48 hours of perforation). Only *Streptococcus pneumoniae*, *Haemophilus influenzae*, and/or *Moraxella catarrhalis* isolated from this sampling technique will be considered interpretable.

H. Statistical Considerations

Draft - Not for Implementation

1. Analysis Plan

- a. Analyses should be performed using two populations. The per protocol population will differ, depending on whether this is a clinical-only or clinical/microbiological study. The intent to treat analysis should include any subject meeting the entry study characteristics.

Both analyses should show consistent results.

- b. Evaluations

Primary efficacy variables include:

- Clinical cure rate at TOC visit
- Overall pathogen bacteriologic eradication rate at TOC without regard to whether the baseline pathogen is susceptible to the study drug (clinical/microbiologic study only)

Secondary efficacy variables include:

- Clinical failure rate at the on-therapy visit
- Overall pathogen bacteriologic eradication rate at TOC where the baseline pathogen is susceptible to the study drug (clinical/microbiologic study only)
- Time to resolution of symptoms
- Persistence of middle ear effusions at the TOC visit
- Clinical response based on age (≤ 2 years old vs. > 2 years)
- Clinical response for patients excluded from the intent-to-treat analysis

Other possible variables include:

- Summary of disease severity at baseline
- Summary of unilateral versus bilateral acute otitis media

2. Sample size

(Reserved)