

FDA Briefing Package
Anti-Infective Drugs Advisory Committee

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Clinical Trial Design in Otitis Media: an Overview

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In the past 25 years the U.S. Food and Drug Administration has published draft guidances on the design and conduct of clinical trials in acute otitis media (AOM). Advances in the understanding of AOM, a better sense of the science of clinical trials, lessons learned from recent drug development programs, and comments from Anti-Infective Drugs Advisory Committee members have highlighted a need to readdress key issues in the design of clinical trials in otitis media. The emergence of pathogens with decreased susceptibility to commonly used antibacterial agents has also added urgency.

The 1998 Draft Guidance to Industry on otitis media specifies that trials in AOM may be superiority or non-inferiority trials. The majority of studies in AOM have been non-inferiority trials. The Guidance suggests two types of designs for trials for the registration of drugs for AOM. The first is a comparative trial in which investigators make the diagnosis of AOM based on strict clinical criteria alone, without the help of microbiologic information obtained by tympanocentesis. The endpoints in this trial are clinical only, based on the resolution of signs and symptoms.

The second kind of study specified in the 1998 Guidance is a microbiology trial that employs tympanocentesis at baseline to establish the bacterial etiology of AOM. This study identifies the specific genus and species of the causative pathogens. The second trial may be non-comparative. The suggested endpoints of this type of trial are microbiologic, based on the eradication or presumed eradication of pathogens, as well as resolution of signs and symptoms in patients with and without documented bacterial disease. The Guidance does not recommend routine repeat tympanocentesis in all patients. However, it encourages repeat tympanocentesis in patients judged to be therapeutic failures, in order to determine bacterial persistence or superinfection.

Several sponsors have performed clinical trials in otitis media based on the 1998 Guidance. The FDA Anti-Infective Drugs Advisory Committee has discussed these trials. Committee members have made the following comments on clinical trial design for otitis media:

- It is difficult to assess efficacy of drugs in non-inferiority trials of AOM with clinical entry criteria and outcomes measures alone. These trials may yield valuable safety information for a new drug product.
- Tympanocentesis at baseline is needed to determine the bacterial etiology of AOM. As the treatment of AOM in clinical practice is almost always empirical, any agent approved should have documented microbiologic activity against all major pathogens.
- A subset of sites may perform a second tympanocentesis after 3-5 days of antibiotic treatment. Only then can we learn whether some agents are less effective than others in sterilizing the middle ear.
- Placebo-controlled trials could be considered in certain populations.

- One should assess clinical outcome at the end of therapy. Longer periods of follow-up are still useful to evaluate resolution of effusion, and relapse/recurrence.
- The populations studied in AOM clinical trials should be relevant and targeted.

Inability to ensure that enrolled patients have otitis due to a bacterial etiology may, in a non-inferiority active-controlled trial, lead to the false conclusion that two drugs are similar in efficacy when, in fact, they may be different. Several studies have documented the lack of precision in clinicians' abilities to diagnose AOM and to discern disease caused by bacteria from other causes. Given this consideration, experts have recommended that evaluation of clinical efficacy of drugs in AOM requires, at a minimum, a single tympanocentesis at baseline. Some Committee members have suggested repeat tympanocentesis on therapy in order to assess sterilization of middle ear fluid. The second tympanocentesis on therapy has been a controversial issue and will bear further discussion at this meeting.

The 1998 Guidance does not distinguish between the severity and chronicity of disease in differing pediatric patient populations within a given trial. Accordingly, most of the trials reviewed by the Agency have not stratified patients by history of recurrence or disease severity. Merging differing outcomes in diverse patient populations may mask important differences in drug efficacy across groups.

The Agency will consider a variety of clinical trial designs for evaluating new anti-infective agents in treating the range of disease in the continuum of otitis medias. FDA staff and invited guests will discuss the pros and cons of different approaches to study design and the options in determining clinical and microbiologic outcomes. We anticipate that the next guidance on AOM will offer a flexible approach to designing an otitis media development program for a given drug.

Attached Articles

- Marchant CD, Carlin SA, Johnson CE et al. Measuring the comparative efficacy of antibacterial agents for acute otitis media: The “Pollyanna phenomenon”. J Pediatr January 1992;120:72-77.
- Chow AW, Hall CB, Klein JO et al. General Guidelines for the Evaluation of New Anti-Infective drugs for the Treatment of Respiratory Tract Infections. Clinical Infectious Diseases, November 1992; vol 15, supplement 1.
- Schwartz RH, Rodriguez WJ. Editorial Correspondence: Criteria for Studies of Antibiotic Therapy for Acute Otitis Media; J Pediatr April 1995;126:Number 4, 677-678.
- U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Guidelines for the Clinical Evaluation of Anti-Infective Drugs-Systemic (Adults and Children), September 1977.
- U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Draft Guidance for Industry: Acute Otitis Media-Developing Antimicrobial Drugs for Treatment, July 1998.
- U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Excerpts from the Division of Anti-Infective Drug Products Points to Consider Document (Acute Otitis Media), October 26, 1992.