Guidance for Industry

Acute Bacterial Otitis Media: Developing Drugs for Treatment

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2008
Clinical Antimicrobial
Revision 1

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TABLE OF CONTENTS

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of acute bacterial otitis media (ABOM). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and designs of clinical trials for drug products to support an indication for treatment of ABOM.[2] It is the intention of this guidance to serve as a focus for continued discussions among the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products and pharmaceutical sponsors, the academic community, and the public.[3] This guidance does not address the development of drugs for other purposes or populations, such as prevention of ABOM or treatment of patients with tympanostomy tubes in place. As the science of this indication evolves, this guidance may be revised as new information accumulates.[4]

This guidance revises the draft guidance for industry *Acute Otitis Media — Developing Antimicrobial Drugs for Treatment* published in 1998. Once final, this guidance will be considered the FDA's current thinking regarding the development of drugs for the treatment of

[1] This guidance has been prepared by the Division of Anti-Infective and Ophthalmology Products and the Division of Special Pathogen and Transplant Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products regulated within CDER unless otherwise specified.

[3] In addition to consulting guidance documents, sponsors are encouraged to contact the divisions to discuss specific issues that arise during the development of antimicrobial drug products.

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

ABOM. It also supersedes, with regard to the development of drugs to treat ABOM, more general guidance issued many years ago (i.e., *Clinical Evaluation of Anti-Infective Drugs (Systemic)* and *Clinical Development and Labeling of Anti-Infective Drug Products*, as well as the joint FDA/Infectious Disease Society of America's *General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products*).[5]

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*. This guidance focuses on specific drug development and trial design issues that are unique to the study of ABOM.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

There have been a number of public discussions regarding the design of clinical trials to study ABOM since the FDA last published draft guidance on the development of antimicrobial drugs for the treatment of ABOM in 1998.[6] These discussions have primarily focused on the appropriateness of noninferiority trial designs for ABOM and other important study design issues such as the following:

- Inclusion criteria
- Application of appropriate diagnostic criteria
- Use of appropriate definitions of clinical outcomes
- Timing of outcome assessments
- Use of concomitant medications
- Role of microbiological outcomes

Important changes from the 1998 draft guidance that are based on these discussions have been incorporated into the appropriate sections below.

[5] Beam, TR, DN Gilbert, and CM Kunin, 1992, General Guidelines for the Clinical Evaluation of Anti-Infective Drug Products, Infectious Disease Society of America and the Food and Drug Administration, Clinical Infectious Diseases, Nov.15, Supplement 1:S5-32.

[6] The design of ABOM clinical trials was the subject of the July 11, 2002, meeting of the Anti-Infective Drugs Advisory Committee. A transcript of that meeting is available at www.fda.gov/ohrms/dockets/ac/02/transcripts/3875T2.doc.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

New drugs being studied for ABOM should have preclinical data documenting activity against the most commonly implicated pathogens for ABOM (i.e., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*).

a. Animal models

Several animal species, including the mouse, rat, and chinchilla, have been used to evaluate antimicrobial activity in vivo. However, with increasing study of the role of genetic factors in the pathogenesis of ABOM and a better understanding of the susceptibility of various strains of mice to bacterial infections, the mouse model has assumed increasing prominence in studying the pathogenesis and treatment of ABOM. Pathological and histological responses to antibacterial treatment have been shown in the previously mentioned species as well as other species.

Although animal models may contribute to demonstrating proof of concept in the treatment of ABOM (or for comparing in vivo activity of different antimicrobials), the results should be carefully interpreted when being used to help design subsequent human studies. Animal studies should not be considered a substitute for the clinical trials in patients with ABOM that should be conducted to evaluate safety and efficacy of the drug.

It is important to understand the pharmacokinetics, metabolism, and distribution of the test drug in the animal being studied to be able to use the data from the animal model to inform the design of studies in other animal models or subsequent clinical studies (e.g., data from animal studies can be one of the components considered in selection of doses that will be evaluated in subsequent clinical studies).

b. Patient-reported outcome instruments

There should be a well-defined and reliable method of assessing patient response in ABOM studies. Sponsors should anticipate the need for appropriate instruments to evaluate clinical response (e.g., well-developed patient-reported outcome (PRO) or caregiver-reported outcome instruments) early in the clinical development process. If an adequate instrument is not available for studying ABOM, we recommend that the new instrument development process begin well in advance of phase 3 clinical trials so that the instrument can be ready for incorporation into the phase 3 protocol.

PRO instruments can be used to measure patient symptoms and self-reported signs; for small children and individuals who cannot respond reliably for themselves, a caregiver-reported

outcome instrument can be used to measure patient signs as observed by the caregiver.[7] Both types of instruments may be appropriate for use in a single study depending on the patient population enrolled.

For more information regarding the development of such outcome measures, see the draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.[8]

2. Definition of AOM/ABOM

Previously, the FDA's clinical definition of *acute otitis media (AOM)* was "inflammation of the middle ear manifested by localized signs or symptoms." To better identify individuals most likely to benefit from antimicrobial therapy, this guidance defines ABOM as "recent or acute onset of inflammation of the middle ear accompanied by the presence of a bacterial pathogen in middle ear fluid." This definition excludes asymptomatic patients with isolated middle ear effusion identified by pneumatic otoscopy (i.e., otitis media with effusion).

3. Efficacy Considerations

FDA review of previous ABOM studies has not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABOM by antimicrobials (a precondition for a noninferiority trial).[9,10] Accordingly, only superiority trials are currently recommended for ABOM studies.[11]

The goal of ABOM clinical trials should be to demonstrate an effect of antibacterial therapy on the clinical course of ABOM caused by *H. influenzae*, *S. pneumoniae*, or *M. catarrhalis*. If pharmaceutical sponsors wish to add additional organisms to this indication, they should provide

[7] It is important to distinguish between signs and symptoms in the context of PRO instruments to avoid any confusion with the use of these terms in the subsequent text. PRO instruments can capture signs or symptoms reported by the patient. A caregiver-reported outcome instrument by definition is not a PRO but may be the best option to capture patient outcomes for younger children who may not be able to directly articulate their subjective state clearly. For example, pain intensity measurement as experienced by a young child can be inferred and reported by a caregiver based on the child's behavior, in which case it is measured as a sign rather than as a true symptom. When *signs or symptoms* are discussed in the following text, in most contexts they include the subjective state of the patient but may be limited to signs (excluding symptoms) when captured by a caregiver rather than a patient.

[8] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

[9] See the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (http://www.fda.gov/cder/guidance/index.htm).

[10] Most previous placebo-controlled studies of ABOM have been clinical studies of AOM where a bacterial pathogen has been presumed; only one prior trial has performed tympanocentesis at baseline (i.e., documenting ABOM at baseline). However, the conclusion of these studies taken together remains that a reliable estimate of the magnitude of benefit that would be expected in a new active-controlled study is uncertain.

[11]Marcy, M, G Takata, P Shekelle, et al., 2001, Management of Acute Otitis Media, AHRQ Evidence Report/Technology Assessment No. 15 (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.chapter.21026).

data sufficient to substantiate the clinical relevance of the particular organism as a pathogen in ABOM.

The number of studies that should be conducted in support of an ABOM indication depends on the overall development plan for the drug product under consideration. If the development plan for a drug product has ABOM as the sole marketed indication, then at least two adequate and well-controlled trials establishing safety and efficacy should be conducted for this indication.

When two studies are conducted for an ABOM indication, we strongly recommend that at least one study be conducted with tympanocentesis performed on all patients (see section III.B.2., Study Population, and section III.B.3., Study Inclusion Criteria). A design with microbiological information on all patients offers the strongest likelihood of success by ensuring that all patients in the primary analysis population have a documented bacterial infection and that an adequate number of patients with each of the common bacterial pathogens has been enrolled (i.e., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*). Microbiological confirmation also permits analysis of treatment response by individual pathogen. Although tympanocentesis is recommended for the second study as well, clinical criteria alone can be sufficient for defining the primary analysis population in a second trial that is conducted as a superiority study. If only a single clinical trial is anticipated in support of an ABOM indication, then tympanocentesis should be performed on all patients in that study.

A single study for an ABOM indication may be appropriate if there are data from other clinical studies demonstrating effectiveness in other respiratory tract diseases and there is additional supportive information such as pharmacokinetic (PK) and pharmacodynamic studies demonstrating concentration of the antibacterial drug in the middle ear fluid at a level expected to be active against the common pathogens causing ABOM. For example, evidence of efficacy from community-acquired pneumonia (CAP) trials may be supportive of a single superiority trial of ABOM because of the overlapping bacterial pathogens and greater seriousness of CAP relative to ABOM.

Currently, there are no surrogate markers accepted by the FDA as substituting for clinical outcomes in ABOM studies. Sponsors who wish to propose a surrogate marker for clinical outcome or the initial diagnosis of ABOM should discuss this with the FDA early in the drug development process.

4. Safety Considerations

There should be sufficient evidence of drug safety from ongoing or completed clinical studies of other respiratory infections in adults before initiating ABOM studies in children, even if ABOM is the sole indication being pursued by a sponsor. Antibacterials with clinically significant toxicity identified in earlier studies should not be considered appropriate for study of this indication. PK studies in children also should be completed before initiating ABOM efficacy studies.

A sufficient number of pediatric patients should be studied at the exposure (dose and duration) proposed for use to draw appropriate conclusions regarding drug safety. Although it may be

possible to derive some of this information from studies of the new drug in adults when exposure is similar or greater than is anticipated for treatment of ABOM, there also should be sufficient evidence of safety in children independent of adults. The total number of pediatric patients needed in a drug development program that includes an ABOM indication should be discussed with the FDA early in the drug development process.

Safety evaluations and assessments specifically should take into consideration the patient populations (e.g., pediatric patients 6 months of age and older) that are likely to be treated for ABOM. Protocols for ABOM should clearly specify the age-appropriate methods to be used to obtain safety data during clinical studies. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Additional safety evaluations may be appropriate because of the preclinical and clinical profile of the specific drug under study. Longer term assessment of adverse events after discontinuation or completion of the antimicrobial also should be considered depending on the specific drug being studied and the potential for long-term or delayed adverse effects.

B. Specific Efficacy Trial Considerations

1. Study Design

Currently, we recommend only superiority trials for ABOM studies. Sponsors who are considering a noninferiority trial for ABOM should justify the proposed noninferiority margin to the FDA as early as possible during protocol development and before study initiation. This situation is discussed further in section III.B.11., Statistical Considerations.

Superiority studies in the treatment of ABOM can consist of the following forms:

- **Double-blinded, placebo-controlled study with a background of *optimized* nonantimicrobial therapy —** This design tests the safety and efficacy of an antimicrobial as an addition to a standardized regimen of analgesic medications compared to the same standardized regimen plus placebo.

- **Delayed versus immediate therapy —** Patients in both study arms receive an *active* therapy, but administration of the comparator treatment is delayed relative to the experimental drug (i.e., one group is started on placebo but then switched to active therapy after a protocol-defined interval). The active therapy can be the same experimental antimicrobial in both study arms. Both groups remain blinded to treatment assignment for the entire study; to demonstrate efficacy, immediate therapy should be superior to delayed therapy.

- **Dose-response —** Patients in each study arm receive different antimicrobial doses (or dosing regimens) together with standardized nonantimicrobial therapy. To demonstrate efficacy, the arm receiving a higher dose (or more intensive therapy) should be superior to the lower dose (or less intensive) regimen.

- **Superiority of the study antimicrobial to another antimicrobial —** Patients in one arm receiving the test drug (with standardized background nonantimicrobial therapy) are compared to patients in a control arm receiving another antimicrobial drug (with standardized background nonantimicrobial therapy). To demonstrate efficacy, the arm receiving the test antimicrobial should demonstrate superiority to the arm receiving the control antimicrobial.

A three-arm study with the experimental treatment group, an active control arm (e.g., an antibacterial drug approved for ABOM), and a placebo-controlled group permits the demonstration of superiority and also can provide risk-benefit information relative to an approved comparator.

At the present time, the FDA does not recognize different forms of ABOM based on disease severity at presentation. However, we recognize that investigators may be less likely to enroll patients presenting with *severe* disease in a placebo-controlled trial than patients with milder symptoms, and that enrollment of hospitalized patients may be incompatible with a placebo-controlled study. We also recognize that treatment of severe disease is where an antimicrobial treatment effect may be greatest. If sponsors wish to study patients with severe disease (or hospitalized patients), we strongly encourage discussion with the appropriate review division regarding protocol design.

2. Study Population

ABOM clinical trials should enroll male and female children, usually from 6 months of age and older. ABOM should be diagnosed by a combination of signs and symptoms, including pneumatic otoscopy and tympanometry/electroacoustic reflectometry at the time of enrollment. Tympanocentesis should be performed at enrollment (i.e., before the initiation of study treatment) in studies where microbiology information is being obtained as part of the study design; if bilateral ABOM is present on exam, tympanocentesis should be performed only on the more involved ear.

3. Study Inclusion Criteria

All signs, symptoms, and test results at baseline (and during time on study) should be recorded. The minimum subset of specific signs and symptoms needed for enrollment should be defined in the study protocol as part of the inclusion criteria for the study.[12]

[12] It is essential that the inclusion criteria for a superiority study be selected to yield a strong likelihood that a patient has disease attributable to a bacterial pathogen; this is particularly important for the success of a trial without mandated tympanocentesis. A protocol also can specify different criteria for the diagnosis of ABOM for different age groups if this improves the overall positive predictive validity for bacterial disease.

At entry, patients also should display a minimum criterion for signs and symptoms to enable a clinically meaningful difference between placebo and active therapy to be detected by the study. For example, if response as measured by a caregiver-reported outcome instrument is the primary study endpoint, then each patient at enrollment should have a minimum decrement in score on this instrument adequate to allow for a possible conclusion of improvement over time.

The following are inclusion criteria that can be used in ABOM trials.

a. Patient history and characteristics

The following patient demographic characteristics should be used for a better chance of selecting patients more likely to have bacterial disease before undergoing baseline tympanocentesis:

- Younger age: less than 5 years
- Fever: temperature greater than 38.5 degrees Celsius
- Biphasic illness: symptoms of ABOM preceded by predisposing infections, such as rhinitis, pharyngitis, and tonsillitis

b. Signs and symptoms

Infants and younger children often present with nonlocalizing symptoms of otitis media; older children are more likely to articulate symptoms referable to the ear. Signs or symptoms that may be present in all children with ABOM include the following:

- Ear pain or earache
- Ear fullness
- Decreased hearing

The following signs may be observed in infants or neonates:

- Head rolling
- Ear tugging
- Ear rubbing

Additional generalized signs and symptoms in infants that are consistent with a diagnosis of ABOM but are otherwise nonspecific include:

- Fussiness or irritability
- Inconsolability
- Decreased appetite
- Sleep disturbance

c. Pneumatic otoscopy

Otoscopic findings considered consistent with ABOM include:

- Bulging or fullness of the tympanic membrane (convexity of the plane of the eardrum), with loss of anatomic landmarks on visualization
- Opacification of the tympanic membrane regardless of color
- Erythema of the tympanic membrane

- Abnormal tympanic membrane mobility on biphasic pneumatic otoscopy; a tympanic membrane in the neutral position or retracted is not sufficient evidence of ABOM as these findings are not specific enough to distinguish the disease from otitis media with effusion

d. Tympanometry

Entry tympanometry and/or electroacoustic reflectometry are recommended for all children at baseline and may help select patients to undergo tympanocentesis. If tympanometry is used, appropriate results for inclusion include either type B or positive pressure peak curves.

e. Baseline tympanocentesis

The microbiological diagnosis of ABOM is based on isolating a bacterial pathogen by tympanocentesis at baseline. Gram stain of the aspirate material with examination for white blood cell (WBC) count also should be performed, with culture as well as antimicrobial susceptibility testing of all bacterial isolates.

Tympanocentesis should be performed only by individuals with expertise in this procedure. Study sponsors should have mechanisms in place to ensure that study centers where this procedure will be performed and the individuals at these centers have sufficient experience and training to perform tympanocentesis.

4. Study Exclusion Criteria

The following patients should be excluded from trials for the treatment of ABOM:

- Patients with otitis externa
- Patients with tympanostomy tubes at the time of study entry[13]
- Immunocompromised patients or patients with other medical conditions that may affect interpretation of the effect of study medications
- Patients on any medications that may affect the interpretation of study outcome (e.g., inhaled steroids)
- Patients with craniofacial abnormalities
- Patients with concomitant infections other than ABOM that may influence the assessment of drug efficacy and safety
- Patients who are allergic to any of the study medications
- Erythema of the tympanic membrane without other evidence of otitis media[14]

[13] Patients with an acute, recent tympanic membrane perforation related to the present episode of ABOM can be enrolled if other entry criteria are met.

[14] Although nonspecific as an isolated finding, the absence of diffuse erythema has a relatively high negative predictive value for bacterial otitis media.

Patients who have received antimicrobial therapy for the current episode of ABOM or within the previous 4 weeks should be excluded unless the trial is designed specifically to study treatment failures.

5. Randomization, Stratification, and Blinding

Patients should be randomized for receipt of study drugs at enrollment. All studies should be double-blinded for study therapy and assessment of outcome unless there is a clearly compelling reason why this cannot be done. PRO endpoints are rarely convincing without double-blinding.

Stratification by age is recommended since younger patients (i.e., younger than 2 years of age) may have lower cure rates than older patients. Other possible stratification factors include unilateral versus bilateral disease, and the presence or absence of otorrhea.

6. Dose Selection

The PK of the drug in children should be established before initiating efficacy studies in children; studies also should assess any PK changes with age. Data from phase 2 dose-ranging studies can be integral to selecting an appropriate dose for phase 3 clinical trials.

Data from studies with tympanocentesis demonstrating drug penetration into middle ear fluid also can be valuable before progressing to phase 3 studies.

7. Choice of Comparators

To date, review of previous placebo-controlled studies of ABOM[15] have not shown a risk to placebo-treated recipients that make future placebo-controlled trials unethical;[16] overall risk from placebo treatment may be similar to that associated with antibacterial therapy since low-frequency severe events (e.g., pseudomembranous colitis or serious allergic reactions) have been observed with almost all antibacterial drugs. The occurrence of common but less-severe adverse reactions (e.g., diarrhea) from antibacterial drugs also can be relevant in assessing the risk-benefit to patients in a placebo-controlled trial where the expected treatment effect may be small. An early clinical assessment for treatment failure at 48 to 72 hours, followed by *rescue* therapy, should be incorporated into the study design so that individual patients are treated at the time a *failure* outcome is assigned; this process may serve to mitigate concerns regarding inclusion of a placebo arm in an ABOM trial.

[15] Studies of AOM and ABOM are used synonymously in this context since earlier studies of ABOM were primarily studies of AOM with a *clinically diagnosed* presumed bacterial etiology.

[16] Most previous placebo-controlled studies of ABOM did not perform tympanocentesis at baseline; therefore, the true incidence of bacterial infection in these trials is unknown. Without this information, the incidence of suppurative complications from untreated ABOM in the setting of a documented pathogen is also uncertain. Similarly uncertain is whether antibacterial therapy would prevent these complications. This concern is also addressed in section III.B.12, Ethical Considerations.

8. Concomitant Medications

All patients should receive effective analgesia for pain associated with ABOM. The use of antihistamines, decongestants, or other therapies is discouraged. However, if other treatments are permitted in the study, their use should be carefully standardized across study groups; the lack of standardization of concomitant medications can introduce an important source of confounding in clinical trials if there are imbalances in receipt of nonantimicrobials between trial groups. Such confounding may occur even if the number of patients receiving concomitant medications is similar between study groups but the reasons for administering concomitant medications differ. Confounding also may occur when the patients in one group who receive concomitant medications differ in baseline characteristics from those patients who do not receive concomitant medications. Therefore, sponsors should make every attempt to control for potential confounders such as concomitant medications. This can be accomplished through a protocol-specified nonantimicrobial background regimen with the dose and frequency of use similar for all patients in the trial; however, the use of standardized, nonantimicrobial therapy in the protocol should be based on experimental evidence that the treatment is effective. At a minimum, the protocol should specify appropriate options for nonantimicrobial therapies during the study.

Assessment of the need for concomitant medications as an endpoint may not be an accurate surrogate for persistent patient signs or symptoms unless the presence of such signs or symptoms is confirmed by a patient- or caregiver-reported outcome tool that shows continued signs or symptoms at the time of administration of the concomitant medication. Effort should be made to capture all concomitant medication use on a patient- or caregiver-reported tool and to relate this information to patient signs or symptoms.

9. Efficacy Endpoints

a. Evaluation of clinical response

The primary emphasis of the study should be the effect of the antimicrobial drug on outcomes that are clinically important to patient symptoms and functioning. Assessment of clinical response at each time point should not be limited solely to signs or symptoms identified at the time of enrollment. For example, if a patient is enrolled with ABOM in one ear and develops ABOM in the opposite ear during therapy while symptoms referable to the first ear are still improving, that patient should not be considered a clinical success. Patient outcome should be based on response per patient rather than per ear (i.e., outcome is measured identically regardless of whether unilateral or bilateral disease is present).

It is likely that in the setting of ABOM studies outcome assessment will include assessment of clinical signs recorded by a caregiver. Caregiver-reported outcome instruments should be limited to observable signs and should exclude items that ask about concepts that can be known only by the patient (e.g., pain intensity).

If improvement or resolution of signs or symptoms is the primary outcome measure of a study, then assessment over time on this measure should be the primary efficacy analysis. An

alternative can be to use response at fixed time points as the primary study endpoint. However, a fixed time endpoint may not be as sensitive a measure of treatment effect as a time-to-resolution analysis. For example, clinical outcome at greater than 7 days after onset of therapy may not show a difference between treatment arms since most patients will be clinically cured by this time regardless of the administration of antimicrobials. Sponsors who choose to use response at a fixed time point as the primary outcome (i.e., as the *test-of-cure* assessment) should provide evidence to support the selection of that specific time point.

Measuring clinical response in an ABOM trial can be approached in two ways: as a binary response (i.e., success or failure based on complete resolution of symptoms) or as a meaningful response as defined by a composite sign or symptom (PRO) scale score.

1. Primary clinical outcome based on complete resolution of symptoms

- *Clinical success.* Clinical success can be documented when a patient exhibits complete resolution of disease-specific clinically meaningful signs and symptoms present at enrollment and the absence of new symptoms attributable to ABOM.

- *Clinical failure.* Clinical failure can be documented as follows:

  – Development of complications of ABOM such as meningitis or mastoiditis.

  – Lack of complete resolution of disease-specific clinically meaningful symptoms or development of new symptoms attributable to ABOM.

  – Treatment with nonstudy antibacterial drugs for ABOM or a related condition.

Patients designated as clinical failures at an early time point should also be designated as clinical failures for all subsequent follow-up visits.

If clinical response is based on complete resolution of symptoms, we recommend that the primary efficacy endpoint be time to clinical success, defined as above for the period from the start of study drug to complete relief of symptoms. The use of an appropriate PRO tool is preferred even when outcome is evaluated categorically as *complete resolution* since this can yield greater assurance that symptoms are being assessed consistently across patients.[17] If an alternative to a PRO is used, the method of assessment should be a well-defined and reliable method of assessing patient response.

2. Primary clinical outcome based on a scale

If a PRO instrument is used for measuring responses that will be based on a scale score, then the score rather than an endpoint of complete symptom resolution should be used as

[17] For more information regarding the development of PRO measures, see the draft guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.* When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

the outcome variable. An outcome scale can be used for describing categorical responses (e.g., *success*, *improvement*, and *failure*) at each time point if the criteria for the categories have been well-developed and validated.[18]

The amount of improvement determined to be clinically meaningful (and, therefore, appropriate for regulatory decisions) should be determined during instrument development and discussed with the FDA before study initiation. Statistically significant differences between comparator regimens can be insufficient for demonstrating benefit if the differences have not been shown to be clinically meaningful.

Nonspecific symptoms may persist in children after treatment for ABOM and possibly confound a study endpoint requiring complete resolution of symptoms; accordingly, use of an accepted PRO response instrument that has been developed with an adequate responder definition that takes into consideration these types of symptoms is strongly recommended in ABOM studies.

b. Clinical relapse or recurrence

Patients who experience clinical improvement without complete resolution of symptoms but then worsen should be considered clinical failures (i.e., there should be no separate category for relapse). Patients who experience complete resolution of symptoms of ABOM for at least 48 hours and then experience further symptoms indicative of ABOM before the early or late follow-up visit should be considered clinical recurrences for that follow-up visit.

Clinical recurrence can be evaluated as a secondary endpoint. Tympanocentesis (or repeat tympanocentesis if performed at entry) in patients who experience further symptoms after success may be valuable, as this would allow a differentiation between patients who may still harbor the initial pathogen compared to patients who have acquired a new pathogen or have a noninfectious etiology for new symptoms, although in both instances this should be considered a clinical recurrence. Bacterial isolates obtained from clinical recurrences should be subjected to an appropriate in vitro method (e.g., pulse field electrophoresis gel) to determine if the original isolate and the isolate obtained from the recurrence episode are indistinguishable.

c. Adverse events or receipt of additional antibacterial therapy

Patients who discontinue therapy because of an adverse event should be evaluated at the time of discontinuation of the study medication. These patients should not be considered withdrawn from the study in terms of overall evaluation; investigators should continue to follow all such patients at study visits as scheduled and continue to record information on both safety and efficacy outcomes. If at the time study medication is discontinued the patient is alive, without complications, and does not receive additional antimicrobial therapy, then the patient should be

[18] If a PRO instrument is used for assessing the primary study endpoint, then it may be possible to use time to reach a specific criterion of clinical improvement as the primary efficacy outcome (i.e., before complete resolution of symptoms). However, use of such a measure as the primary efficacy analysis should be discussed with the FDA before study initiation.

evaluated following the protocol criteria; discontinuation of therapy because of an adverse event should not automatically be considered a clinical failure.

Patients who receive another antibacterial drug while on study drug should be considered failures at the time the second antibacterial drug is administered unless a second unrelated infection has been documented and it is known that the second antibacterial drug does not have activity against pathogens known to cause ABOM.

d. Microbiological response

Although microbiological outcome provides useful information regarding the biological activity of antimicrobials, microbiological outcome is not a direct measure of benefit to patients and, therefore, should be viewed as being supportive but not as a substitute for clinical outcome in a specific trial.[19]

If follow-up cultures are obtained from patients, the cultures can be most useful if samples are obtained after the completion of drug therapy and a sufficient time interval so that drug levels in middle ear fluid will be unlikely to affect culture results (i.e., based on PK and pharmacodynamic considerations). Cultures with no growth obtained while on therapy may represent suppression rather than elimination of organisms.

Although information from repeat tympanocentesis can be valuable if these procedures were performed, we recognize that performing repeat procedures on patients who are clinically well may not be acceptable; accordingly, follow-up microbiological data are likely to be incomplete and unable to fully characterize the concordance of clinical and microbiological outcomes. However, we recommend that investigators perform repeat tympanocentesis in patients who are clinical failures to document bacteriological failure and evaluate the susceptibility profile of any pathogens isolated.

The possibility that there may be a proportion of patients who are clinically cured but who still have bacterial isolates from repeat tympanocentesis calls into question the use of the outcome categories based on inferred microbiological outcomes such as *presumed microbiological eradication*. Such analyses do not add to what is already known from analysis of clinical outcomes; therefore, there are no recommendations for *presumed eradication* in this guidance. The term *eradication* also may be inaccurate, as bacteria may be present but below the level of detection of culture testing; therefore, the term *no growth on culture* is considered to be more accurate.

[19] Microbiological outcomes may be valuable in studies addressing dosing regimens (i.e., where time to no growth on culture is being used as an outcome to optimize dose and/or dosing frequency after clinical benefit has been demonstrated).

10. Study Visits and Timing of Assessments

a. Entry visit

At entry, the investigator should evaluate the patient by performing an appropriate history and physical examination. The information recorded on the case report form during the entry examination should include the following.

- **History and demographic characteristics**

  - Date of visit
  - Age, sex, and weight
  - Underlying medical conditions, if any
  - Current medications, if any
  - History of allergies or allergic symptoms
  - Social environment (e.g., day care attendance), including smoke exposure
  - Number of distinct and well-documented episodes of AOM/ABOM in the previous 12 months and how this information is obtained (i.e., chart review or recall of caregiver); dates, treatment regimens, and outcomes should be recorded

- **Symptoms**

The presence of each symptom, as discussed in section III.B.3., Study Inclusion Criteria, should be documented directly as reported by the patient or caregiver. Baseline signs and symptoms also can be recorded by patients or caregivers in a validated diary (i.e., a PRO or caregiver-reported instrument).

- **Signs at clinic visit**

  - Vital signs, including body temperature measurement.
  - Presence of unilateral or bilateral disease.
  - Otoscopic findings for each ear, including position of tympanic membranes, color, and mobility on pneumatic otoscopy. The absence of tympanic membrane perforation for each ear should be documented.
  - Tympanometry and/or electroacoustic reflectometry for each affected ear.
  - Other laboratory tests (e.g., peripheral WBC count, if obtained).

- **Sample collection**

  For studies where microbiological information is being obtained, the entry visit should include baseline tympanocentesis with culture of middle ear fluid and susceptibility testing of any organisms isolated. All isolates considered to be possible pathogens should be saved in the event that additional testing of the isolate is needed. For microbiological assessment, the investigator should collect the following information:

- Identification of the affected ear sampled (i.e., right or left).
- A description of how the sample was obtained, processed, and transported to the laboratory.
- Identification of the bacterial isolate and serotype if *S. pneumoniae*.[20]
- In vitro susceptibility testing of the isolates to both the study and control drugs. This information should remain blinded while the patient is receiving study medication. In vitro susceptibility testing should be performed by using standardized methods such as the Clinical and Laboratory Standards Institute methods, unless otherwise justified.

b. On-therapy visits

Each patient should have daily on-therapy assessments of signs and symptoms. These assessments can be performed by the investigator during a visit to the investigator's office or by a validated PRO instrument. Regardless of how the assessment is conducted (e.g., interview, interactive voice response via telephone, diary), the questioning of patients or caregivers should be performed in a reproducible and structured way so that any potential biases in the method of questioning do not affect study outcome. The ability to detect differences between study therapies for a time-to-resolution endpoint may be increased if assessments are done more often (e.g., twice daily). Therapy should be continued as described in the study protocol regardless of whether symptoms have resolved; however, patients with resolution of symptoms can be considered as having achieved clinical success if this is a study-defined outcome (i.e., patients with continuing symptoms should be classified as not having achieved clinical success at the measured time point). Investigators should attempt to allow a minimum of 48 to 72 hours on therapy with the study medication before classifying a patient as a clinical failure; accordingly, investigators may wish to include a 48-hour visit to ensure there is not substantial clinical worsening at this time.

Assigning clinical failure and permitting use of rescue antibacterial therapy should be reserved for patients who are worsening on their assigned treatment arm; specific criteria to identify these patients should be included in the protocol. It is important that investigators distinguish patients who are worsening (i.e., where rescue therapy is appropriate) from patients who are slow to improve but may still remain on assigned therapy and thereby achieve clinical success at a later time point.[21] Investigators also may wish to specify a failure endpoint if symptoms have not resolved by a certain day on study, even if the symptoms are not clearly clinically worsening at that time; this may be most objective if defined as a score remaining above a certain threshold for a PRO instrument.

A repeat tympanocentesis can be performed in patients whose therapy has failed and the sample sent for culture and identification and susceptibility testing of isolates. In the case of clinical

[20] The investigator should remain blinded to this information unless the patient has met the criteria for clinical failure.

[21] In a time-to-resolution analysis, a patient should be classified as a success at the time of complete resolution of symptoms. Although the patients that remain are failures at each time point, failure is not carried forward unless a patient has reached a specific failure endpoint (e.g., the need to alter study treatment for rescue therapy). Criteria for failure or the need for rescue therapy should be explicitly outlined in the clinical protocol. Patients should not be unblinded to original study treatment if a criterion for rescue therapy is met.

failure, therapy should then be changed to an appropriate alternative antimicrobial treatment for ABOM, with other therapeutic modifications as necessary. Patients who receive rescue therapy should continue to have the identical protocol-specified assessments as patients who continue to receive their originally assigned treatment.

Investigators should document findings from on-therapy office visits (e.g., history, physical examination, and laboratory test results) on the patient case report form. If the investigator contacts the patient by telephone or by another interactive technology, documentation of the specific questions asked, how they were asked, and the responses given should be captured on the case report form. If a validated diary is used to capture patient symptoms during this study, this information also should be recorded on the patient case report form.

c. Early follow-up visit

The early follow-up visit should occur after completion of all study medication at a time when the drug is expected to clear from the site of infection. For example, if a study drug with a short half-life is administered for 5 days, this study visit can occur on day 7 to 10 after initiation of therapy. At this visit the investigator should perform a focused medical history and physical examination, as well as appropriate laboratory measurements. The investigator also should inquire about adverse events. Evaluation of relapse is discussed in section III.B.9., Efficacy Endpoints. If clinical failure or relapse is suspected, a specimen should be obtained for bacterial culture by tympanocentesis.

d. Late follow-up assessment

The late follow-up assessment should occur 10 to 14 days after the completion of all study medication (e.g., if study drug is administered for 10 days, this assessment can occur on days 20 to 25 after initiation of therapy (unless a drug with a long $t_{1/2}$ has been studied)). For patients with no adverse events noted at the early follow-up assessment and who are clinical successes (i.e., previous resolution of all symptoms), this assessment can be performed by a telephone contact. For patients with adverse events occurring at or after the early follow-up assessment, investigators should perform an assessment that includes a medical history, a physical examination, appropriate laboratory evaluations, identification of any new adverse events, and follow-up on unresolved adverse events. All adverse events should be followed to resolution.

The late follow-up assessment should include questions regarding any symptoms of ABOM to ascertain if late relapse or recurrence has occurred; if clinical failure or recurrence is suspected, a specimen should be obtained for bacterial culture by tympanocentesis.

e. Safety evaluations

The protocol should clearly specify the methods to be used to obtain safety data during the course of the study. Both adverse event information and safety laboratory data should be collected during the study. Age- and sex-appropriate normal laboratory values should be included with clinical measurements when reporting laboratory data. Longer-term assessment of

adverse events after discontinuation or completion of the antimicrobial also can be considered depending on the specific drug being studied.

All patients should be evaluated for safety at the time of each study visit or assessment, regardless of whether the test drug has been discontinued.[22] All adverse events should be followed until resolution, even if time on study would otherwise have been completed.

11. Statistical Considerations

Sponsors should designate the hypotheses to be tested before initiation of the trial. These hypotheses should be clearly stated in the statistical analysis plan and the trial should be powered to detect differences between study arms if group differences exist. If sponsors choose to test multiple hypotheses, they should address issues related to the potential increase in obtaining false positive results (type I error) because of multiple comparisons, either by adjusting the type I error or using a stepwise, closed testing strategy for hypothesis testing. If sponsors use a closed testing hypothesis strategy, they should specify the order of hypothesis testing before initiation of the trial and the method for controlling the overall Type I error rate. These issues should be discussed with the FDA in advance of enrollment in the trial, and should be incorporated into the statistical analysis plan as appropriate.

a. Analysis populations

The following definitions apply to various populations for analyses in ABOM clinical trials:

- **Safety population —** All patients who received at least one dose of drug during the study.

- **Intent-to-treat (ITT) population —** All patients who are randomized.

- **Modified intent-to-treat (MITT) population (also sometimes referred to as microbiological intent-to-treat population) —** When tympanocentesis is performed on patients as defined in the study protocol, this population is all patients who are randomized and who have a pathogen known to cause ABOM isolated at baseline. Patients should not be excluded from this population based upon events that occur post-randomization (e.g., loss to follow-up).

- **Per-protocol populations (also referred to as the *clinically evaluable* or *microbiologically evaluable* populations) —** The population of patients who meet the definition for the primary analysis population (ITT or MITT population) and who follow important components of the protocol as specified (e.g., administration of a specified minimum amount of study medication). Traditionally, adequacy of therapy for a per-protocol analysis population has been defined as patients who have received greater than or equal to 80 percent (or within 80 to 120 percent) of the prescribed dose amount and/or

[22] For specific safety reporting requirements during clinical trials, see the ICH guideline for industry *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (http://www.fda.gov/cder/guidance/index.htm).

dosing regimen. Sponsors should document compliance with dosing (e.g., daily assessment, caregiver or patient diary, urine testing, return of unused drug, or MEMS caps).

The ITT populations in the study should be evaluated as well as the population of patients who follow important aspects of the protocol (i.e., the per-protocol populations) to ensure consistency of results. However, it is also important to note that the per-protocol population analyses are subgroup analyses since they exclude patients based upon events that occur after randomization. Patients in such subgroup analyses may differ by important factors (both measured and unmeasured) other than the drug received; because of this, analyses based on the ITT (or MITT) population should be considered the primary study analyses, with analyses based on a per-protocol population reviewed for consistency of results. Results in both populations should provide evidence of effectiveness.

b. Noninferiority margins

FDA review of previous ABOM studies has not been able to establish a reliable estimate of the magnitude of benefit for treatment of ABOM by antimicrobials; because of this, noninferiority trials are currently not considered adequate to establish evidence of effectiveness for regulatory approval of a new indication for ABOM. For additional information regarding noninferiority studies in antibacterial trials, see the draft guidance for industry *Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval*.[23]

c. Sample size

The appropriate sample size for a clinical trial should be based upon the number of patients needed to answer the research question posed by the study. The sample size is influenced by several factors including the prespecified type I and type II error rates, the expected success rate, and the noninferiority margin (for a noninferiority trial) or the amount by which the study drug is expected to be superior to the control in a superiority trial. Sample size should be based upon the number of patients needed to draw conclusions in the ITT (no tympanocentesis performed) or MITT analysis population.

d. Missing data

There is no single optimal way to deal with missing data from clinical trials. Sponsors should make every attempt to limit loss of patients from the trial. Analyses that exclude patients are subgroup analyses, and patients who do not complete the trial may differ substantially from patients who remain in the trial in both measured and unmeasured ways. Therefore, sponsors should prespecify in the protocol the method of how missing data will be included in the analysis of trial results. Sponsors also should present sensitivity analyses in the final study report such as including all missing patients as failures, including all missing patients as successes, and including all missing data as successes or failures in each study group respectively.

[23] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

Different rates of missing data or differences in the reasons for missing data across treatment arms can be a cause for concern in the interpretation of a clinical trial. If this occurs, it should be addressed in the study report.

e. Interim analyses and data and safety monitoring boards

If interim (or futility) analyses will be performed, they should be specified in the analysis plan. The purpose of the interim analysis should be clearly stated in the analysis; it is important that the interim analysis not affect study conduct and thereby compromise study results. Study data also should be examined at the time of interim analysis for any emerging safety signals. We encourage sponsors to discuss their plans with the review division before initiation of the trial to ensure that the overall study significance tests properly address the effect of interim testing.

Usually, data and safety monitoring boards (DSMBs) are used to evaluate ongoing safety and efficacy issues during clinical trials of diseases with endpoints that measure mortality and/or serious morbidity; however, since these endpoints are uncommon in ABOM studies, a DSMB may not be needed for an ABOM study. Sponsors can still use a DSMB if they choose to do so.[24] If a DSMB is used, a detailed charter with the composition of the committee members and the operational details should be provided for review.

f. Other analyses of interest and secondary endpoints

Sponsors can present secondary analyses on endpoints such as:

- Clinical response in unilateral versus bilateral disease
- Investigator assessment of patient response
- Response based on patient demographics (e.g., age younger than 2 years old versus 2 years old and older)

Analyses of secondary and additional endpoints should be considered exploratory since a trial usually is not designed to address the questions raised by these analyses, either because of multiple comparisons and/or concerns with subgroup analyses. However, the conclusions of such analyses can be strengthened if hypotheses related to these endpoints are prespecified in the protocol, if adjustments for multiple comparisons (maintenance of type I error) are outlined in the protocol, and if the trial is appropriately powered to determine differences between groups related to these variables. Analyses of secondary and additional endpoints can be most helpful for identifying areas for study in future trials.

g. Statistical analysis plan

The sponsor should submit the statistical analysis plan for any phase 3 ABOM study to the FDA before initiation of the trial.

[24] For more detailed guidance, see the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (http://www.fda.gov/cder/guidance/index.htm).

Clinical and microbiological outcomes from blinded studies also can be used for assessing the accuracy of an established or tentative microbiological breakpoint for the treatment under study.

12. Ethical Considerations

Concerns have been expressed in previous discussions regarding ABOM studies that institutional review boards (IRBs) or investigators may consider a placebo-controlled study to be unethical. The general issue of the ethics of placebo-controlled trials is addressed in section II.A.3. (2.1.3) of the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials*. With the possible exception of a superiority study of the investigational antimicrobial compared to another antimicrobial, the other types of superiority studies discussed in section III.B.1., Study Design, of this guidance may involve the withholding of known effective antimicrobial treatment. For such a clinical investigation to be approvable by a local IRB under 21 CFR part 50, subpart D, the risk to children randomized to a comparator arm that involves the withholding of known effective treatment (whether placebo or delayed therapy) must be no more than a minor increase over minimal risk (21 CFR 50.53). Nevertheless, "whether a particular placebo controlled trial of a new agent will be acceptable to subjects and investigators when there is known effective therapy is a matter of investigator, patient, and institutional review board (IRB)/independent ethics committee (IEC) judgment, and acceptability may differ among ICH regions. Acceptability could depend on the specific design of the trial and the patient population chosen…" (ICH E10).

For example, given the specific concern of rare infectious complications that may be associated with nontreatment of ABOM (e.g., mastoiditis or meningitis), the study design for a placebo-controlled trial should include an early clinical safety assessment for treatment failure at 48 to 72 hours.[25] If necessary, effective antimicrobial rescue treatment can be initiated at that point, thus limiting the risk exposure of the children randomized to the placebo-controlled arm of the study. This approach involves the investigator having timely access to unblinded culture results if cultures are obtained via tympanocentesis.

Tympanocentesis should be performed only by individuals with expertise in this procedure. Study sponsors should have in place mechanisms to assure that study centers performing tympanocentesis (and individuals at these centers) have sufficient experience and training to ensure that this procedure poses no more than a minor increase over minimal risk to patients (21 CFR 50.53). Alternatively, the availability of unblinded culture results so that effective antimicrobial treatment can be initiated in response to a treatment failure may provide a direct benefit to the enrolled children and thus be acceptable under 21 CFR 50.52. In addition, targeted therapy based on culture results from repeat tympanocentesis performed to assess clinical failures may offer significant health benefit to the affected child.

Finally, for an isolated single-dose PK study in children, sufficient evidence of drug safety from prior studies in adults would be needed so that the risk exposure for children is limited to no

[25] As noted earlier, review of previous placebo-controlled studies of ABOM have not shown a risk to placebo-treated recipients that make future placebo-controlled trials unethical; overall risk from placebo treatment may be similar to that associated with antibacterial therapy since low-frequency severe events (e.g., pseudomembranous colitis or serious allergic reactions) have been observed with almost all antibacterial drugs.

more than a minor increase over minimal risk (21 CFR 50.53). Once sufficient data are available to select an appropriate dose and duration for the investigational drug, an efficacy trial can include either: 1) a population PK approach to supplement the single-dose PK data, or 2) a single-dose PK study using the initial (or perhaps subsequent) dose of the investigational antimicrobial. Based on a component analysis of risk, the PK component of the efficacy study would be acceptable, depending on the exact study design, either as minimal risk (21 CFR 50.51) or as a minor increase over minimal risk (21 CFR 50.53). If the PK data are used to adjust the dose of the study medication, an IRB may consider this aspect of the study as offering the prospect of direct benefit (21 CFR 50.52).

C. Other Considerations

1. Labeling Considerations

The following is an example of a labeled indication for the treatment of ABOM:

> *"[Drug] is indicated for the treatment of pediatric patients with acute bacterial otitis media due to S. pneumoniae, H. influenzae, or M. catarrhalis."*

2. Antimicrobial Resistance Claims

To date, the FDA has not granted resistance claims for ABOM caused by multidrug resistant *S. pneumoniae*. To obtain a claim for resistant pathogens in ABOM, sponsors should present data from within their clinical trials to demonstrate the clinical effect of in vitro resistance in this disease. Resistance claims should be relevant to ABOM (e.g., amoxicillin resistance is more clinically relevant than penicillin resistance in ABOM since amoxicillin is more commonly prescribed for ABOM than penicillin). Sponsors seeking resistance claims for ABOM are encouraged to contact the review division regarding appropriate study designs for resistant pathogens.

3. Recurrent or Persistent ABOM

Although this guidance does not address unique aspects of clinical trial design for the study of persistent or recurrent ABOM, the principles discussed generally are applicable to clinical trials for persistent or recurrent ABOM. Sponsors seeking an indication for persistent or recurrent ABOM are strongly encouraged to discuss their drug development plans with the FDA before the initiation of clinical studies.