Guidance for Industry

Acute Bacterial Meningitis — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

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GUIDANCE FOR INDUSTRY[1]

Acute Bacterial Meningitis — 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 bacterial meningitis.

II. BACKGROUND

Over the years, the Agency has issued guidance to the pharmaceutical industry on how to design, carry out, and analyze the results of clinical trials for the development of antimicrobials for the treatment of infections in a variety of forms. Guidance has been provided verbally during various industry and FDA meetings, in letters written to sponsors, and in general guidance on related issues. This guidance is the result of efforts to collect all pertinent information and present it in one location. Where appropriate, this guidance contains relevant information from several sources, including *Clinical Evaluation of Anti-Infective Drugs (Systemic)* (1977); IDSA's

[1] This guidance has been prepared by the Office of Drug Evaluation IV, representing the Division of Anti-Infective Drug Products, the Division of Special Pathogens and Immunological Drug Products, and the Division of Anti-Viral Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on developing antimicrobials for the treatment of acute bacterial meningitis. 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.

"Guidelines for the Evaluation of Anti-Infective Drug Products" (1992) (IDSA guidance);[2] *Points to Consider: Clinical Development and Labeling of Anti-Infective Drug Products* (1992) (*Points to Consider*), an FDA guidance on issues related to evaluating new drug applications for anti-infective drug products; and *Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products* (February 1997), a draft guidance discussed at a March 1997 advisory committee meeting on anti-infective drug products, which will be superseded by this guidance once it is issued in final form.

III. ACUTE BACTERIAL MENINGITIS

A. Regulatory Synonyms

This indication has generally been known simply as *meningitis*.

B. Study Consideration

1. Study Characteristics

In pediatrics, a statistically adequate and well-controlled multicenter trial is recommended establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product). Follow-up to determine neurologic sequelae following treatment is recommended to determine final therapeutic effectiveness of a drug product.

In adult meningitis, one comparative or noncomparative trial that establishes equivalence to a previously agreed upon microbiologic eradication rate and clinical cure rate is suggested. The minimally acceptable cure rate should be determined by the particular disease (patient age and microorganisms being studied). Follow-up to determine neurologic sequelae following treatment is also suggested to determine final therapeutic effectiveness of a drug product.

In both pediatric and adult meningitis, adequate microbiologic data and specific human pharmacokinetic/dynamic data supportive of clinical effectiveness in this disease entity should be submitted. Such studies should include, but not be limited to, tissue distribution studies that demonstrate the investigative agent diffuses into cerebrospinal fluid in quantities adequate to achieve and maintain levels of antimicrobial compound equal to or above the expected MIC_{90} of the claimed pathogens for an adequate time period.

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

2. Disease Definition

For the purposes of this guidance document, acute bacterial meningitis encompasses acute bacterial infection involving the meninges, which is caused in most age groups by the following pathogens: *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Other etiologic agents that may be studied include *Streptococcus agalactiae* (Group B streptococcus), *Escherichia coli* and *Listeria monocytogenes* in patients younger than 3 months of age, and the latter pathogen in the elderly. This document is not intended to address meningitis in the following clinical situations:

- Patients with indwelling catheters involving the central nervous system (i.e., VP shunts, ICP monitors)
- Status/post recent neurosurgical procedures
- Status/post recent craniofacial fractures/trauma
- Patients with anatomic defects predisposing to infections of the central nervous system
- Patients who are immunocompromised and in which fungal meningitis is a consideration
- Patients with mycobacterial, fungal, parasitic, or viral infections of the central nervous system

Sponsors are encouraged to consider the development of agents for the treatment of meningitis in these situations, but such studies should be discussed with the FDA prior to study initiation.

3. Recent Developments

Recent advances and changes in the prevention and management of acute bacterial meningitis need to be considered prior to discussing further study details.

a. *Haemophilus influenzae* type B (HIB) Vaccine

The widespread use of the HIB vaccine has led to a dramatic decrease in the proportion of acute bacterial meningitis cases caused by *Haemophilus influenzae*, type B, making *Streptococcus pneumoniae* and *Neisseria meningitidis* the two

most common pathogens in all age groups except neonatal. While the decrease in meningitis caused by *Haemophilus influenzae*, type B has been of definite benefit for the infant and toddler age groups (where *Haemophilus influenzae*, type B meningitis had been the most common pathogen) this decrease is expected to change the clinical status of patients at the time of entry into a clinical trial. Both *Streptococcus pneumoniae* and *Neisseria meningitidis* are more apt to produce fulminant infection in children, with 10-20% of all pediatric patients presenting with concomitant shock and DIC. This severe course was less common with *Haemophilus influenzae*, type B. Accordingly, mortality rates when either *Streptococcus pneumoniae* or *Neisseria meningitidis* are involved are higher than seen with *H. influenzae*.

b. Dexamethasone Use

The use of dexamethasone prior to the first dose of intravenous antimicrobial and then concomitantly for the first several days has become routine in pediatric patients, regardless of the pathogen suspected and/or found. This needs to be considered when designing clinical trials.

c. *Streptococcus pneumoniae* Resistance

Epidemiologic surveys have shown a dramatic increase in the proportion of *Streptococcus pneumoniae* strains with decreased susceptibility to penicillin, third generation cephalosporins, and other broad-spectrum beta-lactams. Due to this shift in susceptibility patterns, and in the inherent difficulty of achieving adequate levels of an antimicrobial agent in the cerebrospinal fluid (CSF), the American Academy of Pediatrics (AAP) issued a guidance in February 1997 (*Pediatrics*, vol. 99, no. 2, pp. 289-299) strongly recommending the empiric use of concomitant vancomycin in all patients with suspected acute bacterial meningitis where *Streptococcus pneumoniae* cannot be ruled out. Although this guidance has not yet achieved the same level of acceptance as the use of dexamethasone, for ethical and IRB considerations, this issue should be addressed when designing clinical trials.

4. Foreign Studies

Due to the overall decrease of acute bacterial meningitis patients in this country as a result of the use of the HIB vaccine, it is anticipated that more and more clinical trials studying this indication will be done outside of the United States. Several caveats need to be considered when doing so:

a. Control agent

The pathogens studied and their susceptibility patterns should be similar to those seen in this country. Particular emphasis should be placed on *Streptococcus pneumoniae*, due to its prevalence and changing resistance pattern.

b. Study Implementation

The standard of care should be similar to that seen in this country. Thus, routine use of concomitant dexamethasone and vancomycin (see Drugs and Dosing Regimen) should be addressed when designing clinical trials.

5. Oral Treatment

Oral relay therapy is usually not considered standard of care for acute bacterial meningitis. In situations where a sponsor is considering this option, this should be discussed with the FDA prior to study initiation.

6. Communication with the Reviewing Division

Because of the impact of recent advances in clinical studies of meningitis, it is strongly recommended that all study protocols dealing with this infection be filed under the IND to allow for interchange between the sponsor and the FDA in a timely manner.

With changes in the quality of pediatric intensive care therapy, use of dexamethasone, and quicker initiation of antimicrobial therapy, it will be more difficult to compare results from clinical trials done currently with historical data. Double-blinded, comparative studies should be conducted when studying pediatric patients. Due to the low prevalence in adults, open label, noncomparative studies could be considered when dealing with adult patients.

C. Inclusion Criteria

The study population on which a regulatory decision is ultimately based will consist of patients meeting the enrollment criteria for clinical and microbiological proven diagnosis: patients with both a clinical presentation consistent with meningitis and microbiologic confirmation of a bacterial pathogen (this will be discussed in full detail later). Due to the seriousness of meningitis when not treated quickly, many patients with suspected meningitis may be enrolled who ultimately will not qualify because of missing culture confirmation. This population should be identified for analysis, and a sample size should be estimated based on this population. All efforts should be made to enroll only those patients in whom an acute *bacterial* etiology is strongly suspected. In

situations where the clinical status of the patient allows for a brief waiting period prior to the administration of antimicrobial agents, the results of a cytospin Gram's stain and CSF analysis can be used as a screening tool for entry into the study. A log of all potential patients should be maintained, but only those with CSF analysis/Gram's stain consistent with a bacterial etiology would be actually enrolled into the study. This would not have to be an absolute limitation, and patients who needed immediate therapy could be enrolled.

Inclusion criteria for enrollment into a meningitis study should consist primarily of nonspecific and specific signs and symptoms consistent with meningitis for the age group being studied.

Presenting signs of meningitis vary by age, with nonspecific findings more common in neonates and young infants. Due to this and the differences in etiologic pathogens, separate protocols should be written for patients less than three months of age, pediatric patients, and adult patients. Nonspecific findings in neonates and young infants include irritability, somnolence, poor feeding, and hypo- or hyperthermia. In older children and adults, change in mental status and/or somnolence is commonly seen.

Specific findings in neonates and young infants are difficult to appreciate. For older children and adults, signs of meningeal irritation, such as headache, nuchal rigidity, and positive Kernig and Brudzinski sign may be present. More severe cases of meningitis may present with lethargy, convulsions, or coma. In recent epidemiologic studies, all components of the classic triad of meningitis (fever, headache, and signs of nuchal rigidity such as Kernig and Brudzinski signs) were present in only 60% of older children and adults who were proven to have acute bacterial meningitis.

D. Exclusion Criteria

(See *General Considerations*)

Patients with foreign bodies within the central nervous system, craniofacial trauma, congenital or anatomic defects predisposing to infections of the CNS, immunocompromised status, as well as those with mycobacterial, viral, fungal, and parasitic meningitis should be excluded from these trials.

E. Drugs and Dosing Regimen

Due to the severity of this illness and the consequences if not treated properly, human trials of a new agent should not start until in-vitro activity against the target pathogens has been demonstrated and there has been demonstration that the drug has had adequate penetration into the CSF, based on animal models and/or human phase 1 studies involving patient volunteers, such as candidates for replacements of VP shunts.

The length of therapy will usually be dependent on the pathogen isolated, and this should be addressed in the study protocol. For a patient to be considered having adequate therapy, the patient should receive at least 80% of the prescribed dose amount and/or dosing regimen, except in situations where the patient is a treatment failure (see below). While this may vary with agents with different half-lives, missing two consecutive doses with most agents should be grounds for incomplete therapy and, thus, a failure.

Test Drug: Lot number and other identifier should be provided (safety, not evaluability recommendation).

Control Drug: While any drug and dosing regimen approved by the FDA may be used, consideration should be given to a regimen considered clinically relevant in the area and patient population where the study is to be conducted.

Concomitant Agents: The use of dexamethasone and/or vancomycin in patients with meningitis is common, and may be required by most U.S. institutional review boards (IRBs). Thus, the protocol should address the use of these agents. For dexamethasone, there are recommended dosing regimens that are used by nearly all centers. For vancomycin, the recent AAP guidelines should be considered. In addition, potential antagonism between dexamethasone and the study drug should be addressed in in-vitro studies.

F. Evaluation

1. Entry Visit

For study assessment, patients should have an entry visit. The following information from the initial visit should be included: date of visit, clinical signs and symptoms of meningitis, duration of illness, recent antimicrobial use for present infection or concomitant infection, vital signs, complete physical examination with as complete a neurological exam as can be done, and disease severity score (the Glasgow coma scale is commonly used). Results of the CSF analysis (including WBC and RBC count, WBC differential, glucose and protein levels), serum laboratory test results (including serum glucose counts), cytospin Gram's stain, and antigen testing results should also be included.

Due to the fact that changes in hearing, developmental status, and neurological status are used as part of the definition of efficacy, it is extremely important to describe the status of the patient in the period prior to the onset of meningitis. Thus, at either the entry visit or at some point early on during the study period, parents should be queried regarding the following (and these must be documented completely): hearing status; developmental landmarks achieved and at what age; if in school, learning or reading disabilities; for older

children, history of hyperactivity; and history of motor dysfunctions.

2. On-Therapy Visit

The patient should have an on-therapy clinical and microbiological assessment on the second day of therapy at least 48 hours after initiation of the study drug. This evaluation should include a repeat CSF culture, cytospin Gram's stain, and fluid analysis. Any organism isolated in the repeat culture should have susceptibility testing performed.

There will be patients who are too critically ill to perform a repeat lumbar puncture. In such situations, a repeat CSF culture, cytospin Gram's stain and analysis should be performed as soon as clinically feasible. The IDSA guidance suggest that patients who have a positive culture in the presence of persistent symptoms should be classified as failures. This is due to the correlation between persistence of organisms and the presence of inflammation in the CNS, with prolonged persistence having been associated with increased rates of adverse events post-therapy.

3. End-of-Therapy Visit

This visit is important in patient management, especially as it relates to decisions regarding the continuation of therapy for a longer period of time. Repeat lumbar punctures are traditionally done in certain age groups at this time (for example, in the neonatal age group or in any patient with the isolation of a Gram-negative pathogen), but this is not required from a regulatory viewpoint. If done, results should be included in the patient's case report form

4. Post-Therapy Visit

In the evaluation of meningitis, the test-of-cure visit actually involves two assessments conducted at different times.

a. Early Post-Therapy Visit

This visit is done at 5 to 7 weeks post-treatment completion, and the following should be evaluated at this visit:

Signs/symptoms of meningitis. If present, CSF fluid should be obtained and analyzed as done at the entry visit.

Audiologic examination. The actual method used should be based on the age of the patient. For patients less than 6 months of age, brainstem auditory evoked

response (BAER) testing should be conducted. Between 6 months and 4 years, audiometry enhanced by visual reinforcement or play can be considered, if the patient is compliant. Otherwise, BAER testing can be utilized. Over 4 years of age, adult audiometry is usually performed. All testing should include a complete, wide range of tones.

Developmental testing. Although basic screening, such as a Denver's test, is commonly used for follow-up by clinicians, for the purposed studies, a complete developmental package should be used and performed by qualified personnel. The package to be used should be discussed with the FDA prior to study initiation.

Neurologic testing. A full neurologic examination should be performed and results fully documented. Details regarding aspects of the neurologic examination that is to be performed should be listed in the study protocol.

All test results should be compared to those found historically to be the baseline for the patient (i.e., prior to the onset of meningitis).

b. Late Post-Therapy/Test-of-Cure Visit

A second follow-up visit for assessment of hearing, development, and neurologic status should be conducted 5 to 7 months after completion of therapy. In addition, any behavioral difficulties (such as learning disabilities or hyperactivity) which have developed since the onset of the entry illness should be documented.

G. Outcome

1. Clinical and Microbiological Assessments

The primary efficacy analysis should be based on the clinical response of the fully evaluable (clinically and microbiologically evaluable) population at the test-of-cure visits. A separate analysis of a clinically evaluable (i.e., not microbiologically evaluable as well) population is not done with meningitis trials.

To be fully evaluable for this indication, patients should have a microbiological diagnosis of acute bacterial meningitis as based on the following permutations of CSF and blood culture, CSF analysis, cytospin Gram's stain and CSF antigen testing results:

a. CSF Culture Positive

Evaluable regardless of blood culture, cytospin Gram's stain, or antigen results.

CSF analysis should be consistent with bacterial meningitis (elevated WBC with a predominance of polymorphonuclear leukocytes, decreased glucose as compared to serum levels, elevated protein level).

b. CSF Culture Negative, Blood Culture Positive

If either the cytospin Gram's stain and/or the CSF analysis is consistent with a bacterial meningitis, such patients should be seen as evaluable. Of note, the blood and CSF cultures should be attained during the same period. All other scenarios would lead to a patient being considered unevaluable.

It is expected that the pathogens listed above would be isolated. Other etiologic bacteria may be considered. In situations where the CSF and blood cultures grow different pathogens, the results from the CSF culture should be used, except for situations where the CSF results are seen as erroneous.

2. Clinical Outcome

a. Clinical Cure

Resolution of the acute signs and symptoms of meningitis at the early post-therapy visit. In addition, at both the early and late-post-treatment visits, hearing, developmental and neurological tests are either normal or consistent with the patient's status prior to onset of meningitis.

b. Clinical Cure with Mild Sequelae

Resolution of the acute signs and symptoms of meningitis at the early post-therapy visit. At the late post-therapy visit (TOC), there is a mild deficit in hearing, developmental, and/or neurologic tests. Due to the potential differences among testing devices used, actual definitions of *mild deficit* should be defined by the sponsor in the study protocol and discussed with the FDA prior to study initiation. Deficits noted at the early visit, but which have resolved by the late TOC visit, should be recorded, but the patient should still be considered a cure. In addition, mild behavioral changes, such as mild learning disabilities, should be included in this category.

c. Clinical Failure

There are several categories to be considered here.

i. Patients who require either additional antimicrobials or change in therapy due to lack of clinical improvement. In cases where therapy is altered due to the presence of a pathogen resistant to study drug(s), the patient should be found unevaluable.

ii. Patients with persistence of pathogen noted on the 24- to 48-hour repeat lumbar puncture.

iii. Prolongation of antimicrobial therapy for a period of time beyond that defined in the protocol.

iv. Patients who have completed a minimum of 72 hours of therapy and die due to meningitis are considered clinical failure.

v. Patients with persistence of signs and symptoms of acute bacterial meningitis necessitating initiation of therapy at either of the post-therapy visits.

vi. Patients with moderate to severe *Sequelae*: Included in this category are deficits noted in hearing, developmental or neurologic testing at the late TOC visit. The actual definitions of *moderate to severe* deficits should be defined by the sponsor for each of these tests and discussed with the FDA prior to study initiation. In addition, behavioral changes that lead to major changes in a patient's life (i.e., severe learning disabilities, loss of short-term memory ability) and any development of seizures should be considered in this category.

vii. Initiation of new antimicrobial therapy for the treatment of meningitis in the time period between the end of treatment and the test-of-cure visits would be classified as a clinical failure.

3. Microbiological Definitions of Cure

The majority of patients will not have a repeat CSF analysis performed off therapy. Thus, the microbiologic outcomes will usually be based on the results from the 24 to 48 hour post-initiation of therapy repeat lumbar puncture, and most patients will fall into the category of *presumed eradication.*

a. Presumed Eradication

No repeat CSF culture obtained, but the patient's clinical status is one of cure at

the TOC visits.

b. Documented Eradication

Repeat CSF culture done off therapy shows no persistence of initial pathogens.

d. Presumed Persistence

Two scenarios are included in this definition:

- A change in therapy was made during the course of study drug therapy due to a lack in clinical improvement, but no repeat CSF culture was obtained at this time.

- Patient required either prolongation or initiation of further therapy due to a lack of clinical improvement noted at the off therapy visits, with no repeat culture being obtained at this time.

e. Documented Persistence

Repeat CSF culture (including the culture to be obtained on study day two) showed persistence of the initial pathogen.

H. Statistical Considerations

(Reserved)