Guidance for Industry

Catheter-Related Bloodstream Infections — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
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Clinical Antimicrobial

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GUIDANCE FOR INDUSTRY*

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I. INTRODUCTION

This is one in a series of guidances intended to assist pharmaceutical manufacturers in developing antimicrobial drug products to treat infections. The information presented in this document will provide most if not all of the information that should be used to plan the necessary clinical studies, design the clinical protocols, implement and appropriately monitor the clinical studies, collect relevant data needed for analysis, and perform the appropriate types and numbers of analyses of the study data. The results of studies planned and conducted in accordance with this guidance are expected to yield information that the Agency can use 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 For general information on related topics, the reader is referred to a draft guidance entitled
Development of Antimicrobial Drug Products —General Considerations (July 1998), which currently is being finalized.

This draft guidance focuses on developing antimicrobials for the treatment of catheter-related bloodstream infections. For purposes of this draft guidance, bibliographic references are provided in endnote format.

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. This draft guidance is the result of efforts to collect all pertinent information on one type of infection and present it in one location.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 "Guidelines for the Evaluation of Anti-Infective Drug Products" (1992) (IDSA guidance); *Points to Consider: Clinical Development and Labeling of Anti-Infective Drug Products*

* 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 catheter-related bloodstream infections. 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.

(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.

III. CATHETER-RELATED BLOODSTREAM INFECTIONS

A. Disease Definition

For the purpose of this guidance, *catheter-related bloodstream infections* are defined as bloodstream infections resulting from an infected vascular access device or contaminated infusate, including central venous catheters (tunneled [e.g., Hickman], subcutaneously implanted [e.g., Porta-cath], and nontunneled), peripherally inserted central venous catheters (PICC lines), midline catheters, vascular dialysis catheters (e.g., Quinton catheters), pulmonary artery catheters, peripheral arterial catheters, and peripheral venous catheters. Not included in this guidance are infections related to or associated with permanent intravascular devices (such as vascular grafts or implantable pacemakers or defibrillators), intravascular transplants (such as porcine cardiac valves), or nonintravascular devices (such as peritoneal dialysis catheters or neurosurgical devices such as ventriculoperitoneal shunts, ICP monitors or epidural catheters).

The most common bacterial pathogens in catheter-related bloodstream infections are also common skin colonizers (with the suspected portal of entry being the actual catheter insertion site in most cases) with staphylococcal species accounting for one-half to two-thirds. Of these, coagulase-negative species predominate, but *Staphylococcus aureus* remains a common cause of these infections.[10] Enterococci, particularly vancomycin-resistant strains, account for 8 percent of all catheter-related bloodstream infections.[1,2] *Candida albicans* and other fungal pathogens have become increasingly important causes of catheter-related bloodstream infections in recent years, accounting for roughly 10 percent of nosocomial bloodstream infections.[3] Gram-negative enterics account for the majority of the remainder, with pathogens such as *Klebsiella* spp., *Enterobacter* spp., and *Serratia marcescens* most commonly seen in patients with such risk factors as recent gastrointestinal or genitourinary tract surgery and/or manipulations.[4] Among neutropenic patients, *Pseudomonas aeruginosa* is a common pathogen.

B. Regulatory Synonyms

These infections are sometimes also referred to as *catheter-related bacteremia*. However, the term *catheter-related bloodstream infection* is preferable, since the latter term emphasizes the need for a diagnosis to be based on both clinical and microbiologic criteria. Terms such as *line sepsis, catheter-related septicemia, primary bacteremia,* and *bacteremia of unknown origin* are not synonymous with the term *catheter-related bloodstream infection.*

C. Study Considerations

1. General Study Characteristics

Two statistically adequate and well-controlled trials are recommended establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product). Generally, superiority trials should be performed when there is no approved comparator, as is the case with this indication at present. In these trials, an evaluable patient should be both clinically and microbiologically evaluable. A single superiority trial of the test drug may be sufficient under the circumstances outlined in the FDA guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998). Two equivalence trials might be sufficient to support approval under certain circumstances, as discussed in section III.1. Trials should be double-blind whenever possible.

2. Scope

The purpose of this guidance is to propose consistent methodologies in the design of clinical trials in which catheter-related bloodstream infections are being studied. More specifically, bloodstream infections resulting from either an infected vascular access device or contaminated infusate will be discussed.

This guidance focuses on bacterial infections, though many of the concepts that will be proposed could apply to fungal bloodstream infections related to intravascular access devices. The guidance focuses on bloodstream infections that have been shown to be directly related to one of the intravascular devices listed. Thus, this guidance is not intended for the study of patients with *bacteremia of unknown origin* or with bacteremia due to a focus of infection other than the intravascular device. Entry of patients into clinical trials evaluating catheter-related bloodstream infections should, in part, depend on excluding another sources of the bacteremia.

This guidance is intended for use in studies in adult patients, but as the clinical experience with catheter-related bacterial bloodstream infections in pediatric patients (including neonates) expands, it is envisioned that this guidance will be expanded to include this age group.

3. Diagnosis

The diagnosis of catheter-related bacterial bloodstream infections is difficult for the following reasons:

a. Lack of pathognomonic clinical signs and/or symptoms

Although these infections are usually associated with the presence of fever, a study of intensive-care unit patients with new onset of fever found that 80 to 90 percent of these fevers were not associated with a documented catheter infection.[5] It has been estimated that 75 to 85 percent of catheters are removed unnecessarily during evaluation of new fever.[5] In one study over 70 percent of documented central venous catheter-related bloodstream infections were not associated with signs or symptoms of local inflamation at the catheter entry site.[6] The absence of specific clinical signs and symptoms associated with catheter-related infection makes the diagnosis and evaluation of such infections difficult.

b. Difficulties with culturable material

When no obvious signs of inflammation at the catheter entry site are seen, the diagnosis of a catheter-related infection depends on either blood cultures drawn through the catheter or cultures of the catheter itself. A diagnosis of catheter-related infection on the basis of blood culture alone (without cultures of catheter hardware) can be made on the basis of quantitative differences between colony counts of a pathogen isolated from a blood culture obtained through the catheter and colony counts from a simultaneously obtained peripheral blood culture. Due to the cost and relative unavailability of quantitative blood cultures, this technique has not been widely used. The most accepted methods of diagnosing a catheter-related infection have involved either quantitative or semi-quantitative cultures of the catheter tip.[5] Thus, removal of the catheter is often necessary to diagnose these infections.

c. Lack of consistency in diagnostic techniques

A recent meta-analysis surveyed the English-language medical literature for the years 1966 to 1994 for studies evaluating techniques in diagnosing catheter-related bloodstream infections.[5] Sixteen different diagnostic methods with 17 variations were described. Few studies have examined methods in similar patient populations, but in those studies that have, large differences were noted in both sensitivity and specificity. Due to such wide discrepancies in the ability of various techniques to accurately diagnose a catheter-related bloodstream infection, it is difficult to pool data from different studies.

Therefore, several standards exist that have been adopted and used by investigators. Enrollment of patients into studies of these infections has depended on microbiologic criteria and on the presence of fever, with secondary emphasis placed on other clinical signs and symptoms. The following criteria have been most commonly adopted:

- All other potential foci must be ruled out.

- Patients without another potential focus who have inflammation and other signs of infection at the catheter insertion site or tunnel and a concomitant positive blood culture are classified as having a true catheter-related bloodstream infection.

- In patients without local signs/symptoms, diagnosis of catheter-related bloodstream infections depends on the material available for culture. A quantitative or semi-quantitative tip culture with growth of a pathogen identical to that in a concomitant blood culture fulfills microbiologic criteria for catheter-related infection.

- In situations where the catheter is not available for culture, paired quantitative blood cultures obtained peripherally and from the catheter have been compared. A 3:1 or 5:1 ratio between colony counts for a pathogen from the catheter-drawn culture and a peripheral culture indicates a catheter-related bloodstream infection.[7,8] New methods, such as comparing times to growth in automated blood culture systems or the use of staining techniques (such as acridine orange) have been proposed as well.

4. Epidemiology

More than 150 million intravascular catheters are purchased annually by clinics and hospitals in the United States, including more than five million central-venous and pulmonary-artery catheters.[7] However, due to the differences in disease definition discussed above, the true incidence of catheter-related bloodstream infections remains unknown. Estimates range from 25,000 up to 400,000 per year.[7,9] Based on bloodstream infection rates reported in large Centers for Disease Control and Prevention studies, the estimate of 400,000 may be closer to the true incidence. Catheter-related bloodstream infections, because of the medical conditions with which they are associated, increase the risk of morbidity (such as prolonged hospital stays)[5] and death. Mortality rates associated with catheter-related bloodstream infections range from 10 to 20 percent. The estimated percentage of all bacterial bloodstream infections in the adult population that are related to a catheter ranges from 5 to 15 percent, though experts in the field believe the incidence to be higher.[10]

5. Therapy

As with diagnosis, the therapy of catheter-related bloodstream infections has involved a wide variety of considerations.

- Catheter removal

When the source of a bacteremic infection is suspected to be a peripheral intravenous catheter, the standard of care has been to remove the line and establish access at a new site.[7,11] For long-term catheters such as PICC lines, central venous lines, and arterial lines recent literature strongly suggests that with certain pathogens, particularly *Staphylococcus aureus*, *Pseudomonas aeruginosa*, Gram-negative enterics, and *Enterococcus faecium*, catheter removal should be the first step in the treatment of the related bloodstream infection. However, for the most common group of pathogens, the coagulase-negative staphylococci, there continues to be debate as to whether catheter removal is necessary. When this group of pathogens is involved, the decision to remove the catheter is highly dependent on individual patient factors. Pathogen factors, such as biofilm production or colony-size variants, may also be important.

- Site of new catheter

When the catheter needs to be removed, the next issue to consider is whether a new catheter insertion site needs to be established or whether a new catheter can be placed into the former insertion site (i.e., changing a catheter over a guidewire). Guidance concerning this matter has not been established. A recent meta-analysis of all published articles dealing with this issue suggests that changing a catheter over a guidewire carries a higher risk of reinfection than if a new site is established.[11] Of note, the increased risk was small and the authors suggested that very large studies would be needed to establish whether this is a significant difference.

- Whether to treat with antimicrobials

Another controversial issue is whether systemic antimicrobial therapy is always needed, and for how long, after a potentially infected catheter is removed, or whether only removal of the focus is needed to clear a catheter-related bloodstream infection. Virulent pathogens and/or those known to readily cause metastatic infections (such as *Staphylococcus aureus*) are treated with antimicrobial therapy after catheter removal. The length of therapy depends on the individual patient's clinical status, co-morbidities and the pathogen. However, with coagulase-negative staphylococci, especially if the focus of infection is a peripheral intravenous catheter, the importance of antimicrobial therapy relative to catheter removal is less clear.

- Follow-up

With certain pathogens, notably *Staphylococcus aureus*, a bloodstream infection due to an infected catheter may lead to distant infections that may not manifest until weeks to months have elapsed (such as osteomyelitis). While such infections can occur after a prolonged time, the literature is unclear about what percentage of patients are expected to have such long-term sequelae and at what point the initiation of antimicrobial therapy for the initial catheter-related bloodstream infection will prevent these late infections.

6. Incorporating Guidance into the Design of Clinical Trials

a. Primary Enrollment and Efficacy Endpoints

Enrollment and efficacy determinations will be driven by microbiologic criteria. However, basic clinical signs and/or symptoms are proposed that would be needed for enrollment and that would be used in the final efficacy analysis. The clinical criteria chosen represent a compromise, recognizing that some patients with catheter-related bloodstream infections may not meet the definitions proposed here.[12] On the one hand, given the controversy as to whether antimicrobial therapy is needed in certain situations, the criteria are strict enough so that only patients who unequivocally require antimicrobial therapy would be enrolled. On the other hand, due to the wide variability in clinical presentations of catheter-related bloodstream infection, the criteria are flexible enough so as not to make enrollment prohibitively difficult.

b. Microbiologic Criteria

Evaluability and efficacy decisions will be based primarily on microbiologic criteria; therefore, the criteria proposed are intentionally strict.

c. Line Removal

The criteria for line removal should be defined prospectively and applied uniformly for all patients within a randomization stratum. If line removal is not required at enrollment, patients requiring line removal more than 72 hours after initiation of therapy because of clinical failure or bacteriologic persistence or relapse should be considered treatment failures.

Changing lines over a guidewire as a substitute for line removal may cause a discrepancy in efficacy rates and is discouraged. If performed as part of the study, criteria for this practice should be specified prospectively and applied uniformly. When this approach is used, a separate subset analysis should be performed for patients whose lines were changed over a guidewire.

d. Inclusion/Exclusion Versus Evaluability Criteria

Due to difficulties in diagnosing catheter-related bloodstream infections, a large proportion of patients enrolled into a study may ultimately be found not to have this infection. On the other hand, strict entry criteria that are based on the presence of a proven catheter-related infection will not allow for the enrollment of patients in whom empiric therapy must be started. Because a major emphasis in the final approval decision will be on the results in the subset of patients with a proven catheter-related

bloodstream infection, sponsors are encouraged to enroll enough patients in whom this infection is proven or strongly suspected.

e. Randomization

The sponsor should decide, prior to study initiation, between a prospective stratification of randomization versus planned, poststudy subgroup analyses. The former approach would be more valuable in a clinical trial when the study population has either proven or strongly suspected catheter-related bloodstream infections at the time of enrollment, so that the evaluability rates are high. The latter approach would be more valuable in a clinical trial in which more severely ill patients are enrolled in whom empiric therapy is started in a large percentage before a catheter-related infection is proven. In such a study, large numbers of patients could be found to be unevaluable, so that subgroup analyses would be more heavily relied on for efficacy analysis. Potential strata to use in either analysis approach include presence or absence of neutropenia, age, and severity of illness (such as stratification by APACHE II scores). Other possible strata that would need to be discussed with the FDA in advance could include type of device (e.g., arterial catheters, PICC lines), use of antimicrobial-impregnated catheters, and pathogen(s) of interest.

D. Inclusion Criteria

To be enrolled, patients should have at least one of the two clinical criteria listed below ***and*** at least one of the microbiologic criteria listed below. However, there will be clinical trials where empiric therapy will be started before microbiologic confirmation. In such situations, at least one clinical criterion should be met for the patient to be enrolled, and the microbiologic criteria should be used as part of the evaluability criteria.

Clinical criteria:

Temperature ≥ 38.0°C or < 36°C, with one of the following:

- WBC count >12,000 or <4,000, or with a differential count showing ≥ 10% band forms
- Tachycardia: Pulse rate > 100 bpm
- Tachypnea: Respiratory rate > 20 breaths/minute
- Hypotension: Systolic blood pressure < 90 mm Hg

or

Signs and symptoms of localized catheter-related infection (tenderness and/or pain, erythema, swelling, purulent exudate within 2 cm of entry site)

Microbiologic criteria:

The concordant growth of the same organism from peripheral blood and one of the following:

- *A blood culture aspirated from a catheter,* as shown by quantitative cultures of catheter-drawn and peripherally drawn blood cultures with a catheter to peripheral blood culture organism ratio of 3:1 to 5:1, regardless of pathogen.[1,4,14,15]

- *A culture of a catheter segment,* as shown by quantitative cultures of the catheter segment where the number of organisms is $\geq 10^3$ CFU/segment, regardless of pathogen[13]; quantitative cultures of catheter-drawn and peripherally drawn blood cultures with a catheter to peripheral blood culture organism ratio of 3:1 to 5:1, regardless of pathogen[5,8,14,15] ; or semiquantitative cultures of a catheter segment (i.e., Maki technique) where the number of colonies of an organism cultured from the catheter tip is > 5 CFU/segment, regardless of pathogen.[16,17]

- *A culture of the interior surface of a catheter hub,* as shown by quantitative cultures of the catheter hub where the number of organisms is $\geq 10^3$ per segment of catheter.[5] This criterion applies to pathogens that are common skin colonizers, such as coagulase-negative staphylococci. For pathogens that are not common skin colonizers (e.g., *Pseudomonas aeruginosa*), concurrent cultures of the interior surface of the catheter hub, regardless of colony count.[18]

- *A culture of a catheter entry site exudate,* as shown by concurrent cultures of the catheter entry site, regardless of pathogen and regardless of colony count.[5, 19,20]

- *A culture of infusate,* as shown by concurrent cultures of the infusate, regardless of pathogen and regardless of colony count.

Definition of *concordant*

For all pathogens, the peripheral blood culture and the catheter-related culture (as outlined above) should have growth of the same species. These species should have either the same pulsed field gel electrophoresis (PFGE) profile or the same antibiogram.[21,22,23,24] For cases in which the pathogen is a common colonizer for which different strains may have identical antibiograms (e.g., coagulase-negative staphylococci),[25] use of PFGE is strongly recommended. Use of a particular method to demonstrate concordance should be supported by data showing that the method is capable of distinguishing between different strains of the same organism, and of distinguishing between contamination and true infection.

E. Exclusion Criteria

The exclusion criteria have been divided into three categories.

1. Exclusion of other endovascular infections:

- Patients with clinical and/or echocardiographic evidence of endocarditis
- Patients with prosthetic cardiac valves
- Patients with vascular grafts
- Patients with septic thrombophlebitis
- Patients without a pre-existing vascular access device with community-acquired bacteremia

2. Exclusion of other infections resulting in bacteremia

- Patients with clinical or radiographic evidence of osteomyelitis
- Patients with skin/skin structure infection, pneumonia, urinary tract infection, joint infection, intra-abdominal infection, or other infection known to be due to the organism cultured from the blood

3. Other exclusion criteria

- Administration of >24 hours of potentially effective anti-microbial therapy within 72 hours of enrollment
- High probability that line removal alone will cure the infection
- High probability of death from an unrelated underlying disease within 14 days
- Hypersensitivity to the study drugs
- Renal or hepatic dysfunction, except as specifically provided for in the protocol

F. Drugs and Dosing Regimens

1. Investigational Agent

Data should be submitted demonstrating that the pathogens to be studied are susceptible in vitro to the study drug, including information from animal models. Because some of the pathogens implicated in catheter-related bloodstream infections can metastasize to various body sites (as seen with *Staphylococcus aureus*), an investigational agent should be shown to achieve adequate concentrations in both serum and various tissues and fluids. Preferably, the investigational agent should be bactericidal against the pathogen(s) of concern.

Studies should be designed to demonstrate that, at the dosing regimen to be studied, the investigational agent achieves and maintains concentrations predicted to inhibit 90 percent of clinical strains of the pathogens of concern (i.e., MIC_{90}); for patients with impaired immunity (e.g., neutropenic patients), achievement of bactericidal

concentrations may be recommended. The concentrations that need to be achieved will depend on the pharmacodynamic parameter most related to the investigational drug's activity (e.g., concentration-dependent versus time-dependent activity).

2. Comparator Agent

The sponsor should clearly specify the comparator to be used in the clinical trial(s). At this time there are no approved agents for this indication and, thus, the sponsor should choose the most appropriate standard of care as the comparative agent(s). This choice should be discussed with the Agency prior to study initiation. The sponsor can consider a dose-response study design. This approach may be problematic when trying to show a dose/efficacy response, given the high efficacy rates seen in clinical studies in which patients with mild-to-moderate severity of illness were treated. A dose-response study design may be most feasible when studying a population of patients with high severity of illness scores.

3. Adjunctive Therapy

With seriously ill patients, adjunctive and concomitant therapies are commonly used, such as vasoactive drugs and anti-fungal agents. The sponsor should make sure that the same standard of care is used in both the study drug and comparator drug arms. In addition, the sponsor should consider any potential antagonistic or synergistic effects due to drug-drug interactions. Such factors may affect not only efficacy rates, but the adverse event profile as well.

4. Duration of Therapy

The duration and timing of therapy should be specified prospectively in the protocol and may be pathogen-dependent. For example, a 14-day course of therapy may be appropriate for more virulent pathogens while a shorter duration of therapy may suffice for infections due to less virulent pathogens. The duration of therapy will also depend on the nature of the study population enrolled, with longer courses anticipated for neutropenic patients, as an example. For evaluation of a therapeutic response the patient should receive at least 80 percent of the intended regimen for at least 72 hours.

5. Switch in Therapy

Depending on the patient population to be studied, oral therapy may be considered, either as the initial therapy or as the relay therapy after several days of intravenous antimicrobial therapy. Criteria for switching from intravenous to oral therapy should be prospectively defined in the study protocol.

G. Evaluation Visits

The following evaluations are recommended. At each of these visits, two sets of peripheral blood cultures should be obtained; in situations where the catheter is not removed, blood cultures through the catheter should be obtained as well. In situations where the initially infected catheter is removed, cultures from the new catheter are not needed unless there is evidence for infection of the new catheter. These visits are:

1. Entry

At the initial evaluation, the following information should be obtained and recorded: vital signs, clinical signs and symptoms, particularly those suggesting local inflammation at a catheter site, type and site of catheter, and laboratory results. Clinical and laboratory data regarding other potential foci of infection should also be obtained and recorded. As described above, peripheral blood cultures and either cultures of the catheter itself or blood cultures drawn through the catheter should be obtained. In addition, cultures of the catheter hub or infusate should be considered, since these represent potential sources of catheter-related bloodstream infection.

2. On-Therapy

At 48 to 72 hours, a formal evaluation should be conducted by the investigator, and a decision should be made whether the drug is showing effectiveness. This decision should be based on results of blood cultures (i.e., whether clearance of the pathogen from the bloodstream has been achieved) and evaluation of the patient's clinical status. Patients who have a change in therapy due to poor effectiveness of the initial regimen should be considered therapeutic failures. In addition, patients who do not have their catheter removed initially, but have their catheter removed at this visit (unless this removal is a pre-planned change), should be considered therapeutic failures.

3. End-of-Therapy

This is an optional visit at which an investigator can decide whether additional therapy is needed or not. If prolongation of therapy is warranted, the protocol should prospectively define how these patients will be analyzed. If an alternative therapy is initiated, these patients should be considered therapeutic failures.

4. Early Follow-up (test-of-cure visit)

This visit should be at least 5 days post-completion of therapy, with a longer period of time planned for study drugs with a long half-life. At this visit, the investigator should also look for clinical signs or symptoms consistent with possible metastatic phenomena (such as joint inflammation, bone pain, or signs of endocarditis). This visit should occur

at a uniform time from baseline for all study groups (an issue when dealing with "short" versus "long" therapy comparisons).

5. Late Follow-Up Visit

The primary purpose of this visit is evaluation for possible metastatic infections. This visit should be considered mandatory for patients in whom a pathogen known for causing late-onset metastatic infections (e.g., *Staphylococcus aureus*) is isolated in the entry cultures. Because the literature is unclear about the appropriate timing of such a visit, a 4-week postcompletion of therapy visit is proposed.

H. Outcome

As noted previously, the major emphasis in the evaluation of efficacy will be on the population of patients who have a proven catheter-related bacterial bloodstream infection. A composite endpoint (i.e., clinical and microbiologic response) at the test-of-cure visit will be the primary endpoint in the final regulatory decision, with differences in all-cause and/or infection-related mortality rates also considered. Clinical and microbiologic outcomes should also be examined separately. In situations where the clinical and microbiologic outcomes differ, possible causes for the discrepancy should be explored in the study report. Secondary endpoints that could be considered include time to clearance of bacteremia, percentage of patients with documented late metastatic sequelae, and development of resistance during therapy.

Analysis of the following populations is suggested:

- Modified Intent-to-Treat

All randomized patients who meet required clinical and microbiologic inclusion criteria at randomization. In addition, subgroup analyses as described in section III.C are suggested.

- Evaluable

All patients who meet required clinical and microbiologic inclusion criteria at randomization; have none of the exclusion criteria; receive at least 80 percent of the study regimen for at least 48 hours; do not receive concomitant antimicrobial therapy for reasons other than treatment failure; do not have discontinuation of assigned therapy solely for adverse events; and have all follow-up evaluations.

The following outcome categories are suggested:

- Cure

Patient shows complete resolution of entry signs and symptoms and negative blood cultures at test-of-cure visit. Patients at risk for late metastatic sequelae (e.g., *S. aureus* osteomyelitis) do not show such sequelae at late follow-up.

- Failure

Patient shows any of the following:

- Incomplete resolution of entry signs and symptoms at test-of-cure
- Clinical deterioration or relapse while on therapy requiring change to alternative therapy
- Persistent or relapsing bacteremia while on therapy
- Death from infection
- Late metastatic infectious sequelae (e.g., osteomyelitis)

Separate reporting of clinical and microbiological outcomes is also recommended.

I. Statistical Considerations

At present, there is no approved drug for this indication for use as a comparator. In such a situation, evaluation of a new drug generally proceeds using one of two approaches. If a drug exists that is a widely accepted standard of care for the indication, the sponsor can use an equivalence trial, provided sufficient activity can be documented in the comparator drug for the given indication. If there is no widely accepted standard of care, or if the efficacy of the standard of care is difficult to document, a superiority design will probably be the best approach.

A superiority trial could take any of a number of forms, including:

- Test drug vs. comparator drug
- Dose response of test drug (e.g., high dose vs. vs. mid dose vs. low dose)
- High dose of test drug vs. low dose of test drug vs. comparator drug

Discussion of the choice of comparator drug and considerations involved in the use of a dose-response design are discussed above in section III.F.

Alternatively, ***two*** equivalence trials might be sufficient to support approval, if the following conditions can be satisfied:

- The sponsor provides an analysis based on a comprehensive review of historical data.
- The analysis supplies convincing evidence about the level of activity that the comparator drug provides in this population. Specifically, this analysis should address how much cure rates would differ between the following groups in a hypothetical clinical trial:

Group 1: Comparator drug(s) + line removal (where indicated) in a population such as that studied in the trial, receiving all background therapy.

Group 2: Line removal (where indicated) in a population such as that studied in the trial, receiving all background therapy.

The analysis should establish a defensible estimate of difference in cure rates between Group 1 and Group 2. Let this difference be denoted δ. The delta used in the sponsor's equivalence trial should be smaller than this value δ, and also be sufficiently small to exclude clinically important differences. Delta should not be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of the planned trial, but may be smaller based on clinical judgment.[*]

The analysis should consider the relative distribution of the pathogens found in the trials, as well as other baseline characteristics.

A line-removal policy will be in effect in both arms of the sponsor's trials; thus, historical data about patients in whom line removal practice is not similar to what will be done in both groups of sponsor's trials is not pertinent to this analysis.

Even when delta is appropriately selected prior to a trial, circumstances of a particular trial, such as poor compliance or the characteristics of the study population, could invalidate the suitability of this delta. Thus, the sponsor should also document that its trial has assay sensitivity (also known as *difference detecting ability*).[*]

J. Review Considerations

(Reserved)

K. Labeling Considerations

(Reserved)

[*] This is discussed in detail in the International Conference on Harmonization (ICH) draft guidance E-10, which is to publish in September 1999.

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