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ASSOCIATE VICE PRESIDENT
US REGULATORY AFFAIRS



March 13, 2000

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

RE: Guidance on developing antimicrobial drugs for treatment of catheter-related bloodstream infections; Docket Number 99D-4328; 64 Federal Register 56799; October 21, 1999

Dear Sir or Madam:

We are writing on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA) and thirteen of the manufacturers of antimicrobial drug products (Astra Zeneca, Aventis, Bayer, Bristol-Myers Squibb, Glaxo Wellcome, Johnson & Johnson, Lilly, Merck, Parke-Davis, Pfizer, Pharmacia & Upjohn, Schering-Plough, and SmithKline Beecham) to comment on the draft guidance "Catheter-Related Bloodstream Infections – Developing Antimicrobial Drugs for Treatment," Federal Register Notice of October 21, 1999 (64 FR 56799). The October 21, 1999 Notice invited written comments on the draft guidance by December 20, 1999. Dr. Renata Albrecht of ODE IV indicated the PhRMA comments would be accepted subsequent to the response date.

PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. PhRMA-member companies are focused on the design, conduct, and reporting of clinical trials that enable regulatory decision-making with subsequent availability of new medicines to improve the health of patients in the United States and worldwide. Investing over \$24 billion a year in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures. As pioneers in the discovery and development of new treatments, PhRMA companies are frequently involved in the scientific questions that inevitably arise from FDA's review and oversight of the development, licensing, and marketing of new drugs and biologics products. Accordingly, PhRMA companies have a significant stake in optimizing the clinical trial requirements being developed for investigating antimicrobial drugs.

99D-4328

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Pharmaceutical Research and Manufacturers of America

the FDA's Division of Anti-Infective Drug Products summarized the general contents of the draft guidance and discussed with the Anti-Infective Drugs Advisory Committee members clinical issues relative to the draft guidance.

The comments and recommendations of PhRMA and fourteen of the manufacturers of antimicrobial drug products are supplied as an attachment to this letter.

PhRMA and its member manufacturers of antimicrobial products would like to express their appreciation for this opportunity to comment on the general draft guidance for industry entitled "Catheter-Related Bloodstream Infections – Developing Antimicrobial Drugs for Treatment." We welcome your responses to our comments.

Sincerely,

A handwritten signature in black ink that reads "Alan Goldhammer". The signature is written in a cursive style with a large, prominent initial "A".

Alan Goldhammer, Ph.D.

Enclosure

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PhRMA AND MANUFACTURERS OF ANTIMICROBIAL DRUG PRODUCTS

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Catheter-Related Bloodstream Infections – Developing Antimicrobial Drugs for Treatment

III. Catheter-Related Bloodstream Infections

A. Disease Definition (p. 2)

It is assumed that a single claim will be granted by organism irrespective of which type of catheter is used. PhRMA requests that FDA confirm that this is the case. PhRMA also requests clarification of the meaning of the phrase “contaminated infusate.”

C. Study Considerations

1. General Study Characteristics (p. 3)

- The requirement for two statistically adequate and well-controlled trials is not consistent with other indications in which two studies are required and has considerable implications as to enrollment numbers and time. The large sample size required and slow enrollment rates anticipated based upon expert review of the proposed entry criteria make this requirement impossible to reach within a reasonable development timeframe. PhRMA suggests that, as in other indications, a single pivotal equivalence study with confirmatory evidence (with a second, smaller supportive study) should be sufficient, especially in circumstances where the drug is being, or has been, studied in other indications (such as supportive data from trials, including bacteremic infections from other sites (e.g., skin/skin structure); this data should be sufficient to provide adequate clinical and microbiological evidence of safety and efficacy.
- That there is no FDA-approved comparator reflects the fact that this is a newly defined indication. For this clinical condition, the usual responsible pathogens, as well as clinically accepted approaches to therapy, are well defined in the literature. Therefore, it is not necessary and may not be possible. PhRMA urges that FDA require a true superiority trial in this patient group, equivalence to a comparator regimen in current use, and as supported by the literature. Although there is currently no drug approved for this therapy, vancomycin may be regarded as the standard of care and therefore a suitable comparator and an equivalence trial design could be appropriate. Another possible comparator is Synercid, especially in institutions with very high levels of VRE infections.
- PhRMA agrees that double-blind study design should be used whenever possible.
- PhRMA recommends that enrollment and efficacy determinations be driven by microbiologic as well as clinical criteria. Clinical criteria should be broad enough so as not to make enrollment prohibitively difficult. Microbiologic diagnosis should reflect common clinical practice in the diagnosis and treatment of catheter-associated infections.

- PhRMA recommends that criteria for line removal be defined prospectively and line changes over a guidewire be looked at as a separate subset analysis.

3. *Diagnosis*

a. Lack of pathognomonic clinical signs and/or symptoms (p. 3)

Fever as a clinical criterion can be a problem with extremes of age, i.e., elderly and neonates, but is acceptable outside these ranges. We would also suggest hypothermia as a criteria in special populations (subjects on hemodialysis or liver transplant recipients), which may also be a specific indicator of infection.

3. *Diagnosis*

b. Difficulties with culturable material (p. 4)

Diagnostic Criteria: Quantitative blood cultures are not readily available in most U.S. and virtually all international hospital laboratories at centers that perform these investigations. The ethics of obtaining the additional phlebotomy volume required to send repeat cultures to a specialized reference laboratory is a concern, especially if the diagnosis is usually made via other means. In addition, there is a potential for discrepancies (contamination or loss in collection/transport to a central lab) which presents a significant issue in the data analysis for the trial. Current clinical practice utilizes positive blood cultures from the suspect catheter paired with peripheral blood cultures as the standard of proof. PhRMA urges that FDA accept this practice. Also, PhRMA urges FDA to consider developing specific guidance for accepting the use of routine blood cultures where time to positivity could be collected.

Certain bacteremias (e.g., coagulase negative) in the setting of no other obvious source of infection may be regarded as catheter-related bloodstream infections. PhRMA recommends that FDA consider adding this.

5. *Therapy*

Site of new catheter (p. 6)

This section is not helpful regarding the site of a new catheter and whether to treat with antimicrobials. Additionally, no advice is given regarding trial conduct. PhRMA recommends that the removal of the catheter and exchange over a guide wire be left to the best clinical judgment of the treating physician, based on individual cases. Suggestions for standardizing the criteria for removal of temporary catheters may be beneficial, but requires more expert input. A post hoc analysis of the success of the strategy of guidewire exchange vs. fresh venipuncture in the microbiological response to treatment may be planned as an additional confirmatory analysis for efficacy.

5. Therapy

Follow-up (p. 6)

PhRMA recommends that FDA provide further clarification regarding this point and its implications for clinical trials.

6. Incorporating Guidance into the Design of Clinical Trials

a. Primary Enrollment and Efficacy Endpoints (p. 7)

Enrollment will also be driven by clinical symptoms, as it is unrealistic to expect microbiology results at the time of enrollment. Therefore, PhRMA recommends that **subjects may be eligible based on presumptive evidence that the clinical signs and symptoms are due to the IV catheter (with the reasonable exclusion of other likely sources) and be considered evaluable for this indication if they meet both clinical and microbiological criteria for IVC-BSI. The primary efficacy analysis subset therefore would be a modified intent to treat subset. An intent to treat analysis would be useful only to evaluate the success of the investigators in correctly predicting the source of the infection and anticipating the probable causative pathogen, and would not add specific information on the efficacy of the drugs under study.**

6. Incorporating Guidance into the Design of Clinical Trials

c. Line Removal (p. 7)

The decision to remove or salvage a catheter depends on multiple patient variables that can not easily be categorized prospectively.

PhRMA suggests the following as more practical alternatives:

A. Non-tunneled (temporary) catheters: including peripherally implanted central catheters (PICC), peripheral IV catheters, and temporary central venous or pulmonary artery catheters, are more likely to be removed or exchanged in the course of treatment.

B. Tunneled (surgically implanted) catheters: including Hickman-Broviac and subcutaneous ports, are more likely to be maintained in the course of treatment, as alternative access is limited and risks associated with surgical removal are not inconsequential.

D. Inclusion Criteria (p. 8)

PhRMA agrees that in order to enroll sufficient patient numbers it is important to enroll patients empirically before blood culture results are known. Clinical criteria as outlined in the document (fever with one or more additional signs or symptoms or localized signs or symptoms) are broad enough so as not to limit enrollment and still minimize enrollment of microbiologically non-evaluable patients.

Quantitative culture results are not available until at least 24-48 hours after the specimens are obtained. FDA should make allowance for enrollment with a preliminary report from 2 blood cultures or 1 blood culture plus catheter segment showing target pathogen (e.g., report of "Gram-positive cocci in clusters"). Expert consensus is that physicians would consider this in tandem with fever or the other specific signs/symptoms of infection as justification for antimicrobial therapy pending definitive microbiological evidence.

Other Microbiology Issues: Due to the delay inherent in the process of susceptibility testing, concordance of isolates is also not often known at the time of enrollment. DNA fingerprinting techniques are not practical in real time for screening evaluable subjects, but may be useful in post-hoc analysis. However, the potential for obtaining > 1 isolate, especially for coagulase-negative staphylococci, from catheter segment cultures raises the possibility that concordance may not be easily demonstrated. PhRMA recommends that FDA provide guidance on how to handle this discordance.

As pointed out in the Background Section of the document, there is no laboratory diagnostic culture method considered the "gold standard" for all intravascular devices. Furthermore, many of these techniques are not routinely used in clinical practice, raising issues of quality assurance if they were to be applied broadly at the large number of sites of a large multi-center trial. The requirement for quantitative cultures could not realistically be accomplished in a central laboratory.

PhRMA suggests, therefore, that the primary analysis be done on the population of clinically evaluable patients with proven bacteremias who have an indwelling intravascular catheter and in whom no other focus of infection has been identified at baseline. Limiting the primary analysis to the smaller subset of patients with concordant peripheral and catheter infections is not consistent with the way patients are generally treated in clinical practice and would seriously decrease the evaluable patient population (<50%) and ultimately increase the required sample size considerably.

PhRMA also suggests that a secondary analysis be done on the population of patients who are otherwise evaluable and who have concordant (genus and species) peripheral and catheter culture results.

There are clearly differences between neutropenic and non-neutropenic bacteremic patients. PhRMA recommends that FDA include additional guidance on the inclusion of neutropenic patients.

Patients with contaminated infusates clearly represent a unique and rare clinical entity. PhRMA recommends that they should not be included in this indication.

E. Exclusion Criteria (p. 9)

Under “**1. Exclusion of other endovascular infections,**” PhRMA thinks that exclusion of subjects with vascular grafts after re-endothelialization (> 6 weeks after surgery) is unnecessary. Literature review and expert opinion suggest that these patients are not considered “high risk” in terms of risk of endovascular infection, but would be likely to receive longer courses of therapy (4 weeks) to avoid this complication. Also, the last bullet requires further classification.

Under “**3. Other exclusion criteria**”, PhRMA thinks that the specific circumstances in which patients should be excluded if there is a high probability that line removal alone will cure the infection should be more explicitly stated. It is difficult to assess the high probability that line removal alone will cure the infection. Finally, PhRMA thinks that exclusion of all patients with renal or hepatic dysfunction requires reconsideration. It is likely that these criteria would lead to large numbers of patients being ineligible for participation in clinical trials.

F. Drugs and Dosing Regimens

1. Investigational Agent (p. 10)

At the end of the first sentence in paragraph 1: “including information from animal models” PhRMA urges FDA to confirm that the plural is intended. PhRMA believes that the thigh model is appropriate. PhRMA urges that FDA provide examples of which fluids/tissues need to be specifically evaluated.

In paragraph 2, PhRMA urges FDA to clarify that the MIC₉₀ will apply to the expected spectrum of the target antibiotic, i.e., if the antibiotic is a narrow spectrum gram positive agent, it would apply only to the gram positive organisms.

3. Adjunctive Therapy (p. 11)

PhRMA believes that the issue of concomitant antimicrobial agents needs to be addressed, for example, where there is only a gram-positive agent, but gram negative organisms may be present. PhRMA recommends that FDA issue a guidance on antimicrobial coverage.

4. Duration of Therapy (p. 11)

This section states that patients should receive at least 72 hours of the intended regimen for the evaluation of a therapeutic response. However, section H. (“Outcome”) states that patients who receive at least 48 hours of therapy will be evaluable. PhRMA urges FDA to clarify this discrepancy. Does it require at least 72 hours to be an evaluable success and 48 hours to be an evaluable failure?

G. Evaluation Visits

2. On-Therapy (p. 12)

All patients should have follow-up peripheral blood cultures 48-72 hours into therapy. PhRMA notes that culture results from the 72 hour on-therapy visit would not be finalized until study day 5-10. (The proposal to make an evaluation on therapy at 48 to 72 hours based on blood cultures is impractical in that blood culture results take one or two days to become available and the patient would have had virtually no therapy.) PhRMA recommends that this suggested visit be analyzed retrospectively only for further clarification of subjects who have evidence of treatment failure but who are indeterminate for the post-therapy test of cure visit (for lack of complete follow-up examination).

Removal of the catheter to be considered as overall treatment failures:

- As noted above, the decision to remove the catheter may be due to multiple factors, including infection. PhRMA recommends that the guidance include specific criteria for infectious causes for removal vs. mechanical causes unrelated to infection (e.g., thrombosis, damage to catheter or hub, subject status).
- For subjects enrolled with preliminary report of "Gram-positive pathogen" from blood only, full case definition and the decision to remove a catheter may only be reached after catheter tip cultures are final (in some cases, at > 72 hours from the time the blood was reported).
- Physicians have difficulty making the decision to remove a tunneled catheter in unstable subjects or subjects lacking alternative vascular access. PhRMA suggests that catheter salvage be analyzed as a separate endpoint from eradication of the target pathogen from the blood stream. This has value to the prescribing physician who wishes to have specific data on the success of the strategy of attempting salvage of surgically implanted lines.

4. Early Follow-up (test-of-cure visit)(p. 12)

The requirement for follow-up blood cultures at the test-of-cure post-therapy visit in asymptomatic patients is not consistent with clinical practice. PhRMA recommends that presumed eradication be considered as a microbiological outcome at test-of-cure.

H. Outcome (p. 13)

PhRMA recommends that presumed eradication be considered a favorable microbiological outcome at the test-of-cure visit. Also, PhRMA recommends that the guidance clarify that if, at the test-of-cure, it is obvious that the test culture is contaminated, i.e., a different organism in an otherwise clinical cured situation, this would not constitute a failure if the investigator agreed. PhRMA supports the Advisory Committee's recommendation at the October 20, 1999 meeting that the

catheter cannot be expected to be decolonized and should be considered as a secondary outcome.

Comparator:

Pharmaceutical manufacturers should not be required to defend the efficacy of well-established agents such as vancomycin, which are approved for bacteremia arising from other sources, because of the lack of specific product labeling to cover this new indication. PhRMA agrees with the limited value of literature review, realizing that the data are retrospective and incomplete, and no large prospective trial results are currently available. However, PhRMA thinks that the consensus of the ID community from years of clinical practice experience will confirm the adequacy of such comparators in the treatment of IV catheter-related bloodstream infections.

I. Statistical Considerations (p.14)

PhRMA requests that FDA provide further guidance on the determination of power and sample size calculation based on anticipated efficacy rates (which range from 65-90% in published literature). Even with expected efficacy rates <90%, sample sizes required to test small deltas are too large to be feasible for this indication. PhRMA thinks that collaborative trials may be the only realistic way to allow study of the limited investigator and eligible subject population.

PhRMA urges FDA to seek the consensus of ID experts and clinicians from other specialty groups (critical care, nephrology, and oncology), in addition to the opinions of the pharmaceutical industry, to make sure that guidance for study designs is not only scientifically robust, but also practical and ethical, according to current clinical standards and principles of good clinical practice.

PhRMA would like to raise the issue that superiority trials could be inappropriate if, as PhRMA believes, vancomycin can constitute an appropriate standard of care for gram positive infections. However, it may not be feasible to generate from the literature the specific requirements to justify equivalence laid out in this guideline, as prospective trials have not been conducted.

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