*Format of Reports To Be Submitted*

Full study reports not previously submitted to the Agency, addressing the issues outlined in this request with full analysis (including assay method validation information), assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

*Response to Written Request*

As per the Best Pharmaceuticals for Children Act, section 3, if we do not hear from you within 30 days of the date of this Written Request, we will refer this Written Request to the Director of the NIH. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission ''PEDIATRIC PROTOCOL SUBMITTED IN RESPONSE TO WRITTEN REQUEST'' in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission ''PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES'' in large font, bolded type at the beginning of the cover letter of the submission. Reports of the studies should be submitted as a new drug application (NDA) or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission ''SUBMISSION OF PEDIATRIC STUDY REPORTS—COMPLETE RESPONSE TO WRITTEN REQUEST'' in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked ''PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES'' in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed to by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call NAME at PHONE NUMBER.

[FR Doc. 04–11062 Filed 5–14–04; 8:45 am]

**BILLING CODE 4140–01–P**

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### National Institutes of Health

### Request for Public Comment on a Written Request Issued by the Food and Drug Administration in the Use of Rifampin for the Treatment of Bacterial Endocarditis Caused by Methicillin-Resistant *Staphylococcus aureus*

**ACTION:** Notice.

**SUMMARY:** The National Institutes of Health (NIH) is requesting public comment on the following Written Request issued by the Food and Drug Administration (FDA) for off-patent drugs as defined in the Best Pharmaceuticals for Children Act (BPCA). The Written Request was referred to NIH by the FDA as required by the BPCA.

The Written Request was developed following formulation of an NIH-generated priority list, which prioritizes certain drugs most in need of study for use by children. The priority list was produced in consultation with the FDA, other NIH Institutes and Centers, and pediatric experts, as mandated by the BPCA. The studies that are described in the Written Request are intended to characterize the safety, efficacy, and pharmacokinetics of the drug for optimum use in pediatric patients.

**DATES:** Comments are requested within 90 days of publication of this notice.

**ADDRESSES:** Submit comments to: Anne Zajicek, M.D., Pharm.D., National Institute of Child Health and Human Development, 6100 Executive Boulevard, Suite 4B–09, Bethesda, MD 20892–7510, telephone 301–435–6865 (not a toll-free number), e-mail *BestPharmaceuticals@mail.nih.gov.*

**FOR FURTHER INFORMATION CONTACT:** Anne Zajicek, M.D., Pharm.D., National Institute of Child Health and Human Development, 6100 Executive Boulevard, Suite 4B–09, Bethesda, MD 20892–7510, telephone 301–435–6865 (not a toll-free number), e-mail *BestPharmaceuticals@mail.nih.gov.*

**SUPPLEMENTARY INFORMATION:** The NIH is providing notice of Written Requests issued by the FDA, and is requesting public comment. On January 4, 2002, President Bush signed into law the Best Pharmaceuticals for Children Act (BPCA). The BPCA mandates that NIH, in consultation with the FDA and experts in pediatric research, shall develop, prioritize, and publish an annual list of certain approved drugs for which pediatric studies are needed. In response to this list, the FDA then issues a Written Request to holders of the New Drug Application (NDA) or abbreviated New Drug Application (aNDA) to request that pediatric studies be performed in order to provide needed safety and efficacy information for pediatric labeling. If the Written Request is declined by the NDA/aNDA holder(s), the Written Request is referred to NIH, specifically the NICHD. A Request for Proposal (RFP) is then issued based on the Written Request, and proposals are reviewed by a peer-review process for contract award. In order to assure that the most appropriate pediatric studies are delineated in the RFP, public comment of the Written Requests for the use of Rifampin for the treatment of bacterial endocarditis caused by methicillin-resistant S. aureus in pediatric patients is hereby requested by the NIH.

Dated: May 11, 2004.

**Duane Alexander,**

*Director, National Institute for Child Health and Human Development, National Institutes of Health.*

**Rifampin Written Request**

*Dear Contact:* To obtain needed pediatric information on this active moiety, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from studies in pediatric patients described below. These studies investigate the use of rifampin for the management of infectious bacterial endocarditis in pediatric patients.

*Background and Rationale*

Infective endocarditis (IE) is a serious, life-threatening infection that requires hospitalization. The frequency of IE in hospitalized pediatric patients reported in the literature varies widely. The most widely quoted estimates are 55 to 78 cases of IE per 100,000 pediatric hospital admissions (PHA) but rates as low as 22/100,000 PHA and as high as 200/100,000 have been cited in the literature. Most of these estimates are individual hospital-based retrospective reviews. In a larger survey of 26 major cardiovascular medical center hospitals, Kaplan et. al. reported an average 11 cases of IE per center per year.

There are no published population-based national incidence data of IE in the pediatric population in the United States. The U.S. Hospitalcare Cost and Utilization Project (HCUP) reported 1012 pediatric hospitalizations for endocarditis in the year 2000, of which 657 were coded as acute/sub-acute bacterial endocarditis. Other literature suggests that the frequency of IE in the pediatric age population seems to be increasing primarily due to the improved survival rates of children who are at increased risk for endocarditis, such as those with congenital heart disease and hospitalized newborn infants. An increased use of indwelling central venous catheters in the pediatric population may also be a contributing factor in the possible increasing frequency of pediatric IE.

Although IE occurs relatively infrequently in the pediatric population, it is a serious condition associated with considerable morbidity and mortality and the incidence of IE may be increasing. Mortality estimates for patients with IE reported in the literature range from 10 to greater than 40 percent. IE due to S. aureus is usually associated with higher mortality rates than IE due to other common bacterial etiologies. A recent study reported a mortality rate of 42% within 3 months of diagnosis in patients with prosthetic valve IE due to S. aureus.

In children, staphylococci are a frequent cause of IE. Staphylococcus aureus is the leading cause of acute bacterial endocarditis in children. S. aureus and coagulase negative staphylococci are frequent causes of IE associated with prosthetic heart valves, prosthetic material, and indwelling vascular catheters.

Increasing rates of antimicrobial resistance in staphylococci have made treatment of serious staphylococcal infections more difficult. In 2000, 55% of S. aureus isolates in hospitalized patients reported to the national nosocomial infection surveillance system were methicillin resistant. Coagulase negative staphylococci are usually methicillin resistant, especially in the setting of endocarditis occurring within one year of cardiac surgery.

A recent scientific statement from the American Heart Association provides treatment guidelines for pediatric patients with staphylococcus endocarditis. For native valve endocarditis due to methicillin-resistant staphylococci, the guidelines recommend treatment with vancomycin with or without gentamicin for the first 3 to 5 days of therapy. For staphylococcal endocarditis on prosthetic cardiac valves or other cardiac prosthetic material, the guidelines recommend treatment with a regimen of vancomycin and rifampin with the addition of gentamicin for the first two weeks of therapy. The AHA guidelines also discuss the role for a combined medical-surgical approach to the management of S. aureus prosthetic valve endocarditis. The AHA guidelines represent recommendations from an expert panel based upon evidence derived largely from clinical studies in adults.

There is incomplete information about dosing, pharmacokinetic (PK) parameters, effectiveness, and safety of rifampin in the treatment of staphylococcal endocarditis in children and no adequate and well controlled clinical trials have been performed in children. Rifampin is not currently indicated for the treatment of staphylococcal endocarditis in the FDA-approved package labeling.

*Types of Studies*

A single trial to evaluate the safety and efficacy of rifampin in the pediatric population when used in the treatment of infective endocarditis due to methicillin-resistant S. aureus (MRSA) or coagulase negative staphylococci. Patients who are enrolled are to be stratified by:

(a) Patients with native valve endocarditis due to MRSA.

(b) Patients with a prosthetic heart valve or other prosthetic cardiac material and endocarditis due to either MRSA or coagulase negative staphylococci.

Different protocol-specified antimicrobial therapy may be used in the study for the native valve endocarditis (stratum ''a'' above) and prosthetic material endocarditis (stratum ''b'' above). Within each stratum, the group receiving rifampin plus other protocol-specified antimicrobial therapy will be compared to the control group of the same stratum not receiving rifampin (*i.e.*, receiving only the ''other protocol-specified antimicrobial therapy'').

This study must also include a sub-study describing the pharmacokinetics of oral and intravenous rifampin in children with endocarditis who are ages:

(1) 1 month to <2 years.

(2) 2 years to <6 years.

(3) 6 years to <12 years.

(4) 12 years to 16 years.

Full rifampin plasma concentration versus time profiles, using sparse sampling, will be determined for each group to characterize the pharmacokinetics of rifampin. [Relevant FDA guidance documents regarding pharmacokinetic evaluation are available at the FDA Web site (*http://www.fda.gov/cder/guidance/index.htm*).

It is recognized that although a single study is specified above, it may be administratively preferable to submit a separate study protocol for each of the strata mentioned above (*i.e.* native valve endocarditis or prosthetic material endocarditis). This is also acceptable as fulfillment of this request.

*Objectives*

- To evaluate in the pediatric population the safety and efficacy of intravenous rifampin, followed by oral rifampin, when used in combination with other protocol-specified antimicrobial therapy in the treatment of staphylococcal endocarditis in children. The two groups of children to be studied are (a) children with native valve endocarditis due to methicillin resistant S. aureus, and (b) children with prosthetic material endocarditis due to methicillin resistant S. aureus or coagulase negative staphylococci.
- To describe the pharmacokinetics of intravenous and oral rifampin in pediatric patients with staphylococcal endocarditis.

*Study Design*

The proposed study will be a randomized, multicenter, active-controlled trial, designed to test superiority of rifampin plus other protocol-specified antimicrobial therapy compared to the ''other protocol specified antimicrobial therapy'' in the absence of rifampin (*i.e.*, the ''control'' antibiotic regimen). Patients to be enrolled will be pediatric patients (ages 1 month to 16 years of age) with native valve endocarditis due to MRSA or prosthetic material endocarditis due to MRSA or coagulase negative staphylococci. The study will evaluate the efficacy of rifampin in combination with other protocol-specified antimicrobial therapy (the experimental group) compared to an identical regimen without rifampin (the control group). The design of the study could specify a different antibiotic regimen to be used in the control group for each stratum, [*i.e.*, the strata of pediatric patients with native valve endocarditis could receive a different protocol-specified treatment regimen than patients with prosthetic material endocarditis (*e.g.* the use of different antimicrobial agents and/or a different treatment duration)]. However, within each stratum, the treatment regimen for the rifampin-containing (experimental) group would be identical to the control regimen except for the addition of rifampin. Rifampin will initially be

administered intravenously, with a switch to oral rifampin at a time specified and justified in the protocol.

Pediatric patients will be stratified at enrollment as having (a) native valve endocarditis due to MRSA or (b) endocarditis in the setting of a prosthetic valve or other prosthetic cardiac material. Each stratum will be analyzed separately, with the study being statistically powered to evaluate the effect of rifampin on outcome for each stratum separately. (As noted earlier, each stratum may be considered as a separate study and two separate protocols may be submitted in fulfillment of this Written Request.)

Treatment regimens selected for the active control arm of each stratum must be justified by the sponsor.

Based on published pharmacokinetic studies, it is expected that rifampin dosing in pediatric patients will be approximately 5 mg/kg intravenous every 12 hours and 10 mg/kg orally every 12 hours. If the study enrolls pediatric patients who may be expected to have different pharmacokinetic characteristics from the patients who were enrolled in earlier published studies (*e.g.*, children of certain other ethnicities outside the United States), then additional pharmacokinetic data may be necessary prior to enrollment of these patients. This additional pharmacokinetic data would be necessary to ascertain the appropriate dose for these subjects that would approximate the same exposure as 5 mg/kg IV every 12 hours and 10 mg/kg PO every 12 hours used in previous studies.

*Indications To Be Studied*

Rifampin in combination with other protocol-specified antimicrobial therapy will be studied in pediatric patients aged 1 month to 16 years for the treatment of (a) native valve endocarditis due to methicillin resistant S. aureus (MRSA) or (b) endocarditis in the setting of prosthetic cardiac material due to either methicillin-resistant S. aureus (MRSA) or coagulase negative staphylococci.

*Pediatric Age Groups in Which Study Will Be Performed*

The study will include the following age groups.

(a) 1 month to <2 years.
(b) 2 years to <6 years.
(c) 6 years to <12 years.
(d) 12 to 16 years.

*Number of Patients*

The study will enroll a sufficient number of patients such that it is powered to detect a statistically significant effect attributable to the addition of rifampin to the active control arm regimen. The study must be powered to test significance for each enrollment stratum independently, *i.e.*, there should be separate statistical testing for subjects with native valve endocarditis and subjects with prosthetic material endocarditis. Efficacy results for the two strata should not be pooled.

*Pharmacokinetics Sub-Study*

A subgroup of patients across both strata should be studied to characterize the pharmacokinetics of single dose or multiple dose rifampin administration for both the oral and intravenous forms for each age grouping described above. A minimum of 8 pediatric patients should be studied for each age range (approximately 32–40 overall). Patients should be reasonably distributed between the sexes.

*Inclusion Criteria*

- The protocols must include and justify a reliable diagnostic method (*e.g.* Duke clinical criteria) for enrolling pediatric patients with (a) native valve endocarditis due to MRSA or (b) prosthetic material endocarditis due to either MRSA or coagulase negative staphylococci.
- Microorganisms: Positive blood culture(s) to document infection with methicillin-resistant S. aureus (for native valve endocarditis or prosthetic material endocarditis) or coagulase negative staphylococci (for prosthetic material endocarditis).

*Exclusion Criteria*

- Alternative etiology for endocarditis (protocol defined)
- Hepatic or renal dysfunction of moderate or greater severity (protocol defined)
- Pediatric patients with a known hypersensitivity to rifampin or any of the protocol-specified antibiotic regimens
- Patients who are pregnant or who are sexually active using oral contraceptives as birth control will be excluded from enrollment
- Anyone with glucose-6-phosphate dehydrogenase (G6PD) deficiency shall be excluded from the study
- Anyone who is taking a drug which adversely interacts with rifampin (protocol defined)

*Study Endpoints*

- The primary efficacy endpoint must be specified and justified in the protocol(s). The primary efficacy endpoint will include both a clinical and a microbiological component. The following definitions of clinical cure and microbiological eradication are adapted from the 1992 IDSA/FDA guidelines for evaluation of anti-infective drugs for the treatment of IE.
- Clinical cure—''the resolution of all signs and symptoms of disease is observed after a course of therapy.''
- Bacteriological eradication-defined by at least two or more negative blood cultures at one month after completion of therapy. The primary efficacy endpoint will require both clinical cure and bacteriologic eradication in order for the patient to be considered a cure. Deaths should be included as treatment failures within the primary endpoint. Any patient who relapses (defined in the guidelines as ''blood cultures that become negative during treatment and remain so for a specified period post-treatment but subsequently become positive for the original pathogen'') should have their bacteriologic outcome tabulated under bacterial persistence. The study protocol must address disposition and plans for the analysis of subjects who receive surgery during the study.
- Mandatory secondary endpoints will include all-cause mortality, time to last positive blood culture, and relapse-free survival after completion of therapy. Secondary endpoints may also include time to negative blood cultures (*e.g.*, time until blood cultures are negative for at least 3 consecutive days), time to resolution of fever (*e.g.*, being afebrile for at least 48 hours), normalization of laboratory values such as C-reactive protein, erythrocyte sedimentation rate (ESR), and white blood cell count. The study must monitor and report the antimicrobial susceptibilities of all bacterial isolates obtained in this study.
- Pediatric patients with native valve endocarditis will be followed for at least 3 months after completion of therapy for safety and efficacy endpoints. Pediatric patients with prosthetic material endocarditis will be followed for at least 6 months after the completion of therapy for safety and efficacy endpoints.
- Pharmacokinetics substudy: A rifampin plasma concentration versus time profile, using sparse sampling, will be determined for each patient. Characterization of concentration-time profiles, and determination of relevant rifampin PK parameters (to the extent possible), for example, clearance (CL), volume of distribution (Vd), elimination half-life (T 1/2), maximum concentration (Cmax), time to maximum concentration (Tmax), and area under the plasma concentration-time curve (AUC).

*Drug Information*

Rifampin Dosage Forms

- *Intravenous:* 600 mg Rifampin, sodium formaldehyde sulfoxylate 10mg, and sodium hydroxide to adjust pH.
- *Oral:* 150 mg or 300 mg capsules can be compounded as per FDA-approved package labeling to a concentration of 10mg/ml oral suspension.

Route of Administration. Initially, intravenous in all studies with protocol-specified switch to oral formulation of rifampin based on protocol-specified criteria (*e.g.*, after the patient has stabilized and can tolerate oral administration).

*Drug Specific Safety Concerns*

Routine safety assessments, such as vitals signs, weight, serum chemistry, and monitoring for adverse events must be collected at baseline and at intervals throughout the study. Monitoring should be appropriate for detecting adverse events, including but not limited to hepatotoxicity, renal toxicity, hemolytic anemia, gastrointestinal effects, and seizures. Subjects should be maintained on protocol-specified monitoring even if the experimental or control regimen is discontinued, *i.e.*, consenting subjects should remain on study regardless of therapeutic course after enrollment. Compliance and drug status (*i.e.*, whether the subject is on or off protocol-specified therapy) must be monitored throughout the study. All efforts should be made to minimize loss to follow-up of study patients.

*Statistical Information, Including Power of Study and Statistical Assessment*

The study must have a detailed pre-specified statistical analysis plan appropriate to the study design and outcome measures. The study must be adequately powered (at least 80% power) to detect a statistically significant treatment effect on the primary endpoint at a significance level of $p < 0.05$ (two sided test) for each stratum, *i.e.*, (a) native valve endocarditis due to methicillin-resistant S. aureus, and (b) prosthetic material endocarditis due to methicillin resistant S. aureus or coagulase-negative staphylococci. If two separate studies are submitted, each will be properly powered for the primary endpoint. The assumptions for the sample sizes proposed in the protocol should be clearly stated with appropriate references. Interim analyses should also be included, as should the role of a Data Safety and Monitoring Board.

Descriptions of the PK parameters to be obtained must be provided. Demographic and safety data will be tabulated, and a descriptive analysis of safety data will be provided.

*Labeling Changes That May Result From These Studies*

Appropriate sections of the rifampin product labeling may be altered to incorporate the findings of these studies, including recommended pediatric dosing, treatment of endocarditis, pediatric pharmacokinetics, and safety information in children.

*Format of Reports To Be Submitted*

Full study reports with analysis, assessment, and interpretation, not previously submitted to the Agency addressing the issues outlined in this request will be submitted. Pharmacokinetic study reports should include analytical method and assay validation, individual drug and/or metabolite concentration-time data and individual pharmacokinetic parameters.

In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

*Time Frame for Submitting Reports of the Studies*

Reports of the above studies must be submitted to the Agency on or before September 30, 2007. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

*Response to Written Request*

As per the Best Pharmaceuticals for Children Act, Section 3, if we do not hear from you within 30 days of the date of this Written Request, we will refer this Written Request to the Director of the NIH. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission ''PEDIATRIC PROTOCOL SUBMITTED IN RESPONSE TO WRITTEN REQUEST'' in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission ''PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES'' in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a new drug application (NDA) or as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission ''SUBMISSION OF PEDIATRIC STUDY REPORTS—COMPLETE RESPONSE TO WRITTEN REQUEST'' in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked ''PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES'' in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed to by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call NAME, Project Manager, at PHONE NUMBER.

[FR Doc. 04–11063 Filed 5–14–04; 8:45 am]

BILLING CODE 4140–01–P

## DEPARTMENT OF HOMELAND SECURITY

### Coast Guard

**[USCG–2004–17768]**

### Chemical Transportation Advisory Committee

**AGENCY:** Coast Guard, DHS.

**ACTION:** Notice of open teleconference meeting.

**SUMMARY:** This notice announces a teleconference meeting of the Subcommittee of the Chemical Transportation Advisory Committee (CTAC) on the National Fire Protection