Guidance for Industry

Streptococcal Pharyngitis and Tonsillitis — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

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Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573, or from the Internet at http://www.fda.gov/cder/guidance/index.htm.

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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Streptococcal Pharyngitis and Tonsillitis
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 streptococcal pharyngitis and tonsillitis.

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

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[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 streptococcal pharyngitis and tonsillitis. 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.

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 "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. STREPTOCOCCAL PHARYNGITIS AND TONSILLITIS

A. Regulatory Synonyms

Synonyms include *upper respiratory tract infection due to Streptococcus pyogenes.* Although *Points to Consider* refers to this as "STREPTOCOCCAL PHARYNGITIS" the indication has been granted as "PHARYNGITIS AND TONSILLITIS DUE TO ...." However, it should be clear that the present document is intended to provide guidance on the development of antimicrobials for bacterial causes of pharyngitis and tonsillitis, which for all practical purposes are caused by streptococci.

Pharyngitis and tonsillitis are defined as acute inflammations involving the posterior pharynx and the tonsillar pillars. The infection may be caused by viruses or bacteria. The most common bacterial cause of pharyngitis and tonsillitis is group A beta-hemolytic streptococci. For regulatory purposes, it has been customary to request the actual species be identified (i.e., *Streptococcus pyogenes).*

B. Study Considerations

A statistically adequate and well-controlled multicenter trial should be performed establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product). Any product with an absolute eradication rate at test of cure of <85% should not ordinarily be approved as a first line therapy for this infection. Although the primary effectiveness parameter in this study should be microbiologic eradication, the study should establish the general correlation between clinical cure and bacterial eradication in these patients. In studies of this infection, patients should be clinically and microbiologically evaluable.

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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.*

In addition, adequate microbiologic data and specific human pharmacokinetic/dynamic data supportive of clinical effectiveness in this disease entity should also be submitted. Such studies should include, but not be limited to, tissue distribution studies that demonstrate the investigative agent diffuses into tonsillar tissues in quantities adequate to achieve and maintain tonsillar tissue concentrations equal to or above the expected MIC_{90} of the claimed pathogen for an adequate period of time.

If an applicant chooses to perform more than one adequate and well-controlled trial in this indication (e.g., to establish a sufficient overall safety database for the product), specific pharmacokinetic/dynamic data relative to this indication should not ordinarily be necessary.

C. Inclusion Criteria

Male and female patients of any age may be enrolled; adult patients should be studied (or analyzed) separately from pediatric patients.

For inclusion, patients should have a *clinical* diagnosis of streptococcal pharyngitis (acute pharyngitis and/or tonsillitis) based on history and physical examination, including a full ear, nose and throat examination. Documentation of signs and symptoms characteristic of pharyngitis and tonsillitis should include the following: a sore and scratchy throat, pain on swallowing (odynophagia), temperature, chills and/or fever. The pharyngeal mucosa should be erythematous to fiery red, and a thick exudate should cover the pharynx and tonsillar area. Uvular edema may be noted. Cervical adenopathy should be present and commented on. A white count over 12,000 may be present. Strains of *S. pyogenes* that elaborate erythrogenic toxin may cause a scarlet fever rash of the face and skin folds, red tongue and prominent papillae (strawberry tongue).

To enter the study, the patient should have documentation of some or most of the above signs and symptoms at entry and a positive antigen and/or culture. At a minimum, there should be documentation of at least one sign and one symptom that would be considered clinically convincing of pharyngitis.

> *Note*: The clinical picture may not distinguish *S. pyogenes* infection from viral or other causes of pharyngitis.

The *microbiological* diagnosis of streptococcal pharyngitis is based on the culture results from a specimen typically obtained from the posterior pharynx, the tonsillar pillars. A rapid test for streptococci is often used for screening purposes: Its sensitivity and specificity are not as reliable as culture; therefore, the screening test results should be confirmed by culture.

Documentation should include the presence of *Streptococcus pyogenes* at baseline. The organisms should be susceptible to the study drug(s). The presence of other organisms/pathogens

may be recorded.

D. Exclusion Criteria

(See also *General Considerations.)*

Patients who are known carriers of *Streptococcus pyogenes* should be excluded.

E. Drugs and Dosing Regimen

The patient should receive within 80-120% of the prescribed dose amount and/or dosing regimen. Dosing should be documented as should compliance (diary or urine test for latter). If a patient received 72 hours of therapy and is not doing well, the patient may be classified as a failure.

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

Control Drug: Although any drug and dosing regimen approved by the FDA may be used, consideration should have been given to a regimen considered clinically relevant in the area where the study was conducted.

F. Evaluation

1. Entry Visit

The following information from the initial visit should be included in the patient record: date of visit; clinical signs and symptoms of present episode of streptococcal pharyngitis; results of the clinical examination including ears, nose, throat, culture, and antimicrobial susceptibility testing and laboratory test results.

2. On-Therapy Visit

If the patient is considered to be failing therapy, the drug is stopped and the patient is prescribed another antimicrobial. If the patient is seen for the on-therapy visit, findings from this visit (e.g., history, physical examination, laboratory test results) should be documented in the patient record. If the patient is contacted by telephone, documentation of specific questions asked and responses given should be included in the record. This visit is strongly recommended for good study conduct, but its absence should not serve as the only reason for exclusion from evaluability.

Note: IDSA recommends a 3- to 5-day, on-treatment visit (and allows for the option of making this assessment via telephone call) and weekly thereafter until the patient is asymptomatic.

3. End-of-Therapy Visit

Not applicable (see Test-of-Cure) Visit

4. Post-Therapy (Test-of -Cure) Visit

This visit should occur approximately 14 to 18 days after the start of therapy; for a 10-day course of therapy this would be 4 to 8 days after completion of therapy. The results of the clinical evaluation, including status of all presenting signs and symptoms as well as emergence of any new signs and symptoms of pharyngitis and/or tonsillitis should be documented. Results of the culture and antimicrobial susceptibility testing should be documented.

Note: The IDSA recommends a visit at 4 to 7 days post therapy.

5. Late Post-Therapy Visit

This visit should occur approximately 38 to 45 days after the start of therapy; for a 10-day course of therapy this would be 28 to 35 days after completion of therapy. The purpose of this visit is to assess whether patients may have relapsed or are carriers of *S. pyogenes*, or whether they have developed sequela of the infection such as nephritis or carditis. Again, the results of the clinical evaluation, including status of all presenting signs and symptoms as well as emergence of any new signs and symptoms of pharyngitis and tonsillitis as well as results of culture and susceptibility testing should be provided, if tested.

Note: IDSA recommends a visit at 2 to 4 weeks to assess for carditis or nephritis.

A summary of the procedures and observations at each visit is presented in the chart below:

	VISIT			
EVALUATION STUDY DAY	ENTRY DAY 1	ON-RX(a) DAY 3-5	TEST OF CURE DAYS 14-18	LATE POST(b) DAYS 38-45
Informed Consent	X			
Medical History	X			
Physical Exam	X			
Culture and susceptibility	X	X(a)	X	X
Clinical evaluation	X	X	X	X
Laboratory tests	X		X	
Serology	X			X
Drug Compliance(c)		X	X	

[a] This visit can be an office visit or can be done by telephone. The information obtained should be recorded in the patient case report form.
[b] This follow-up visit should be requested and available for approximately one-half of the patients (see text below).
[c] Urine test, drug count or diary should be used.

G. Outcome

1. Clinical Outcome

A patient who has signs and symptoms of the infection at entry, meets inclusion and exclusion criteria, is compliant with the dosing regimen and returns for the test-of-cure visit 10 to 14 days after the first day of the study.

- *Clinical Cure*: Patient meets above criteria and has resolution of signs and symptoms at the test-of-cure visit. No antibiotics (other than per protocol) were given.

- *Clinical Failure*: Patient has persistent signs or symptoms of streptococcal pharyngitis (including the appearance of the new ones). Also, patients who receive additional antimicrobials or whose antimicrobial therapy is changed are considered failures.

Clinical outcome at the late visit is aimed at evaluating post-streptococcal sequela of carditis and nephritis. Comments about the status of signs and symptoms (e.g., cure, recurrence) of the acute infection may be made, but constitute a secondary endpoint.

2. Microbiological Outcome

A patient who has *Streptococcus pyogenes* isolated from a throat (tonsillar pillar) culture taken at baseline, who meets inclusion and exclusion criteria, is compliant with the regimen and returns for the test-of-cure visit at 14 to 18 days after the first day of treatment.

- *Presumed Eradication*: A bacterial outcome should be extrapolated from a clinical outcome in this indication.

- *Documented Eradication*: The absence of the entry pathogen from the test-of-cure culture.

- *Presumed Persistence*: A bacterial outcome should not be extrapolated from a clinical outcome.

- *Persistence*: Presence of the original pathogen of culture in the test-of-cure culture. Assessment can be done at the late post-therapy visit and constitutes a secondary endpoint.

- *Carrier*: Positive culture for *S. pyogenes* at the late post-therapy visit in a patient whose signs and symptoms have resolved with treatment and did not reappear.

- *Recurrence*: Positive culture for *S. pyogenes* at the late post-therapy visit following a negative culture at the test-of-cure visit.

- *Continued Eradication*: Negative culture for *S. pyogenes* at both the test-of-cure visit the late post-therapy.

H. Statistical Considerations

The main analysis to be performed is on the set of patients who have clinical evidence of pharyngitis and tonsillitis and who have a pathogen isolated at baseline from a throat culture and a repeat culture taken 14 to 18 days relative to the first day of treatment.