Guidance for Industry

Uncomplicated Urinary Tract Infections — Developing Antimicrobial Drugs for Treatment

DRAFT GUIDANCE

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GUIDANCE FOR INDUSTRY[1]

Uncomplicated Urinary Tract Infections 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 uncomplicated urinary tract infections. A separate document addresses development of antimicrobials for the treatment of complicated urinary tract infections and pyelonephritis.

II. BACKGROUND

Over the years, the Agency has issued guidance to the pharmaceutical industry on how to design, carry out, and analyze the results of clinical trials for the development of antimicrobials for the treatment of infections in a variety of forms. Guidance has been provided verbally during various industry and FDA meetings, in letters written to sponsors, and in general guidance on related issues. This guidance is the result of efforts to collect all pertinent information and present it in

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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 uncomplicated urinary tract 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.

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. UNCOMPLICATED URINARY TRACT INFECTIONS

A. Regulatory Synonyms

A number of synonyms have been used in the past in discussions of uncomplicated urinary tract infections, including *acute uncomplicated UTI*, *cystitis*, *acute cystitis*, and *dysuria-frequency syndrome*.

In *Points to Consider*, the recommendation was to use two broad categories of labeling for anti-infective drugs in the treatment of infections of the urinary tract (UTI):

1. Uncomplicated Urinary Tract Infections
2. Complicated Urinary Tract Infections and Pyelonephritis

The 1992 IDSA guidance (pages S216-S227), in contrast, lists 5 categories under "Entry criteria for studies of UTI":

1. Acute uncomplicated UTI in women
2. Acute uncomplicated pyelonephritis
3. Complicated UTI and UTI in men
4. Asymptomatic bacteriuria
5. Recurrent UTI (antimicrobial prophylaxis)

The working definition for this disease is: A clinical syndrome in women characterized by dysuria, frequency, and/or urgency in combination with pyuria and bacteriuria. There is no known underlying renal or urologic dysfunction or obstruction.

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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.*

B. Study Considerations

A statistically adequate and well-controlled multicenter trial should be carried out that establishes safety and effectiveness (i.e., similar or superior effectiveness to an approved product). Although, generally, the primary effectiveness parameter in this study should be microbiologic outcome at 5 to 9 days after the cessation of therapy, the study should establish the general correlation between clinical cure and bacterial eradication in these patients.

In addition, adequate microbiologic data and specific human pharmacokinetic/ pharmacodynamic data supportive of clinical effectiveness in uncomplicated urinary tract infections also should be submitted. Such studies should include, but not be limited to, tissue distribution studies that demonstrate that at the dosing regimen requested in the NDA, the investigative agent diffuses into urine in quantities adequate to achieve and maintain urine levels equal to or above the expected MIC_{90} of the claimed pathogens for an acceptable period of time.

If an applicant chooses to perform more than one adequate and well-controlled trial in uncomplicated urinary tract infections, specific pharmacokinetic and pharmacodynamic data relative to this indication should not ordinarily be necessary, though clearly it is of interest.

If the dosage and duration of therapy are the same for complicated urinary tract infections and effectiveness in complicated urinary tract infections is established as described below for similar microorganisms, a statistically adequate and well-controlled trial, performed at at least two different centers with no more than 55% of the patients from any one center, should be sufficient to establish effectiveness in uncomplicated urinary tract infections. In this instance, microbiologic and pharmacokinetic/pharmacodynamic studies are unnecessary because the safety and effectiveness of the drug in complicated urinary tract infections, a closely related indication, has already been established.

Any pathogen listed on the complicated infection label should be incorporated into the label for the uncomplicated infection claim, if the pathogen is generally accepted to be associated with uncomplicated urinary tract disease. This suggestion is not intended to suggest that similar dosing regimens for uncomplicated and complicated urinary tract infections should be studied. Applicants should determine the most effective and least toxic dose for each indication.

C. Inclusion Criteria

- Non-pregnant adult females.
- Clinical signs and symptoms of a UTI (e.g., dysuria, frequency, urgency, supra-pubic pain) with onset of symptoms $\leq$ 72 hours prior to study entry.

- One positive pre-treatment clean-catch midstream urine culture within 48 hours of enrollment in the study, defined as $\geq 10^5$ CFU/mL.

- In-vitro susceptibility testing of the uropathogen to test and control drug.

D. Exclusion Criteria

(See also *General Considerations*.)

- Males.

- Women who are pregnant, nursing, or not using a medically accepted, effective method of birth control. If an antimicrobial agent is to be studied for the treatment of UTI in pregnant women, this proposal should be justified, the risk/benefit expectations explained, and the issue presented to the division.

- Three or more episodes of acute uncomplicated UTI in the past 12 months.

- Patients with evidence of factors predisposing to the development of urinary tract infections, including calculi, stricture, primary renal disease (e.g., polycystic renal disease), or neurogenic bladder.

- Patients with onset of symptoms 96 hours or more prior to entry.

- Patients with a temperature $\geq 101^0$ F, flank pain, chills, or any other manifestations suggestive of upper urinary tract infection.

- Patients with known or suspected hypersensitivity to the test or control drug.

- Patients who received treatment with other antimicrobials within 48 hours prior to entry.

E. Drugs and Dosing Regimens

Treatment duration may range from single-dose therapy to 3 to 10 days, depending on the drug regimen. Any drug approved for the treatment of UTI may be used as the comparator; however, for the purpose of conducting an adequate and well-controlled study, the comparator agent should be one that continues to have an acceptable safety and efficacy profile in the population to be tested and one that should facilitate study blinding and study evaluation.

F. Evaluation

The following table gives an overview of the evaluation visits and the procedures to be performed at each of the planned visits.

	VISIT			
ASSESSMENT/ OBSERVATION	**1 Baseline Day 0***	**1A[a] On-therapy**	**2 5-9 Days Post-therapy**	**3 4-6 Week Post-Therapy**
Inclusion/Exclusion	✓			
Informed Consent	✓			
Medical History	✓			
Physical Examination	✓		✓	✓
Vital Signs	✓	✓	✓	✓
Clinical Evaluation	✓	✓	✓	✓
Pregnancy Test[b]	✓			
Bacteriology Quantitative Urine Culture and Susceptibility	✓	✓	✓	✓
Urinalysis	✓	✓	✓	✓
Hematology	✓		✓	
Chemistry	✓		✓	
Adverse Events	✓	✓	✓	✓

* Visit days are recorded throughout this report as shown above; Day 0 = Day of first dosing.

[a] Visit 1A is an optional visit. Either a telephone contact or a visit is conducted at this time.

[b] A serum pregnancy test should be performed on all females of child-bearing potential.

1. Entry Visit

The procedures listed in the above table should be performed and the information from these should be documented in the patient consent form.

2. On-Therapy Visit (*optional*)

3. End-of-Treatment Visit

An evaluation at the end of treatment should not be considered as a substitute for the test-

of-cure evaluation. This visit is unnecessary.

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

This visit should take place at 5 to 9 days after the completion of treatment, the procedures listed in the above table should be performed, and the results should be documented in the case report form.

5. Late Post-Treatment Visit

This visit is useful for the assessment of patient relapse after treatment. However, the absence of this visit does not exclude the patient from the primary evaluation of efficacy. It is recommended that a minimum of 50% of the patients be assessed for relapse.

G. Outcome

1. Clinical Outcome

The patient should be a female with clinical signs and symptoms of an uncomplicated urinary tract infection, who meets the inclusion and exclusion criteria, has complied with the dosing regimen, and returns for the 5- to 9-day test-of-cure visit.

- *Clinical Cure:* Resolution of signs and symptoms at the 5- to 9-day test-of-cure visit and no use of additional antimicrobial therapy.

- *Clinical Failure:* No apparent response to therapy, persistence of signs and symptoms of infection, or reappearance of signs and symptoms at or before the 5- to 9-day test-of-cure visit, or use of additional antimicrobial therapy for the current infection.

2. Microbiological Outcome

The patients should meet the clinical criteria listed above and should also have a pathogen isolated from the urine specimen obtained at baseline. The quantitative count of the pathogen should be $\geq 10^5$ CFU/mL.

- *Eradication*: A urine culture, taken within the 5- to 9-day post-therapy window, shows that all uropathogens found at entry at $\geq 10^5$ CFU/mL are reduced to $< 10^4$ CFU/mL.

- *Persistence*: A urine culture, taken any time after the completion of

therapy, grows $\geq 10^4$ CFU/mL of the original uropathogen.

- *Superinfection*: A urine culture grows $\geq 10^5$ CFU/mL of a uropathogen other than the baseline pathogen during the course of active therapy.

- *New Infection*: A pathogen, other than the original microorganism found at baseline at a level $\geq 10^5$ CFU/mL, is present at a level $\geq 10^5$ CFU/mL anytime after treatment is finished.

3. Clinical and Microbiological Outcome at 4 to 6 Weeks Post-Therapy

The purpose of this visit is to assess the relapse rates in the two arms of the study. The microbiological and clinical outcome definitions are presented below:

Clinical Outcome

- *Sustained Cure*: All pre-therapy signs and symptoms show no evidence of resurgence at the follow-up visit 4 to 6 weeks after the last dose of drug.

- *Failure*: Patients carried forward from the 5- to 9-day post-therapy visit.

- *Relapse:* Signs and symptoms, absent at the 5- to 9-day post-therapy visit, re-appear at the 4- to 6-week post-therapy visit.

Microbiological Outcome

- *Long-term, Sustained Eradication*: A urine culture taken within the 4- to 6-week post-therapy window shows that all uropathogens found at entry at $\geq 10^5$ CFU/mL are still reduced to $< 10^4$ CFU/mL.

- *Persistence*: A urine culture taken any time after the completion of therapy, grows $\geq 10^4$ CFU/mL of the original uropathogen. These patients are carried forward from the 5- to 9-day post-therapy visit.

- *Superinfection*: A urine culture grows $\geq 10^5$ CFU/mL of a uropathogen other than the baseline pathogen during the course of active therapy, with symptoms of infection as previously stated.

- *Recurrence:* A urine culture grows $\geq 10^4$ CFU/mL of the original uropathogen taken anytime after documented eradication at the 5- to 9-day post-treatment visit, up to and including the 4- to 6-week post-therapy

visit.

- *New Infection*: A pathogen other than the original microorganism found at baseline at a level $\geq 10^5$ CFU/mL is present at a level $\geq 10^5$ CFU/mL anytime after treatment is finished.

4. Intent to Treat

(Reserved)

H. Statistical Considerations

The main analysis in the conduct of urinary tract infection studies should be based on patients who have a documented bacterial infection, based on the isolation of a urinary pathogen at a colony count of $\geq 10^5$ CFU/mL of urine sample taken at the entry visit. If more than one pathogen in present in the urine, then each one should be isolated at a count of 10^5 CFU/mL to be considered a valid pathogen. The primary efficacy endpoint is the eradication of the baseline pathogen from the 5- to 9-day test-of-cure visit.

I. Review Issues

(See also *General Considerations*.)

A complete presentation of the microbiology data should be made, including the type of specimen (e.g., midstream urine), date of specimen collection, any/all organisms isolated on culture, the actual colony count for each pathogen isolated, and susceptibility testing results.

J. Labeling

The labeling for the drug product would reflect the indication and organisms for which adequate data were presented. Information about observed eradication rates may be included in the labeling under the CLINICAL STUDIES section to further delineate the activity of a particular antimicrobial.