

# Guidance for Industry

## Complicated Urinary Tract Infections and Pyelonephritis — Developing Antimicrobial Drugs for Treatment

### *DRAFT GUIDANCE*

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Comments and suggestions regarding this draft document should be submitted within 90 days of publication of the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573,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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## **GUIDANCE FOR INDUSTRY<sup>1</sup>**

### **Complicated Urinary Tract Infections and Pyelonephritis — 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 complicated urinary tract infections and pyelonephritis developing antimicrobial drugs for treatment.

#### **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 one location. Where appropriate, this guidance contains relevant information from several

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<sup>1</sup> 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 antimicrobial drugs for the treatment of complicated urinary tract infections and pyelonephritis. 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.

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sources, including *Clinical Evaluation of Anti-Infective Drugs (Systemic)* (1977); IDSA's "Guidelines for the Evaluation of Anti-Infective Drug Products" (1992) (IDSA guidance);<sup>2</sup> *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. COMPLICATED URINARY TRACT INFECTIONS AND PYELONEPHRITIS**

#### **A. Regulatory Synonyms**

This indication has been approved under the name *urinary tract infections, including pyelonephritis*. In *Points to Consider*, the recommendation was to use two broad categories of labeling for anti-infective drugs in the treatment of urinary tract infections (UTIs):

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

In contrast, the IDSA guidance (pages S216-S227) 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)

This document focuses on complicated urinary tract infections and pyelonephritis. A separate document addresses the development of antimicrobials for the treatment of uncomplicated urinary tract infections.

#### **B. Study Considerations**

1. Study Characteristics

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<sup>2</sup> This guidance appeared in IDSA's (Infectious Disease Society of America) supplement to *Clinical Infectious Diseases*, formerly *Reviews of Infectious Diseases*.

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A statistically adequate and well-controlled trial should be conducted establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product). The primary effectiveness parameter in these studies should be microbiological outcome. The study should establish the general correlation between clinical cure and bacterial eradication in these patients. Pathogens listed in the INDICATIONS AND USAGE section of the product labeling should be recognized etiologic agents of the infection.

In addition, a comparative or noncomparative trial that establishes statistical equivalence to the success rate of the approved agent in the first complicated UTI trial, or to an effectiveness rate agreed upon with the reviewing division should be conducted. In this trial, the applicant should demonstrate that the patient demographics, the disease severity, the exclusion/inclusion criteria, the evaluability criteria, and the primary effectiveness parameters were not substantively different from those in the adequate and well-controlled first trial. The trial should be performed by different investigators than those involved in the first trial and the sites should represent geographically different areas.

Pyelonephritis can be either an uncomplicated or complicated clinical disease. The Agency suggests that it be studied with complicated urinary tract infections because dosing regimens for pyelonephritis and complicated urinary tract infections are routinely similar. If an insufficient number of patients with pyelonephritis are studied and successfully treated with the investigative agent (minimum: 30 patients/arm/study), the listing should not include pyelonephritis.

### 2. Disease Definitions

*Complicated UTI* is defined as a clinical syndrome in men or women characterized by the development of the systemic and local signs and symptoms of fever, chills, malaise, flank pain, back pain, and CVA pain or tenderness, occurring in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization. Usually, one or more of the following conditions are present that increase the risk of developing an infection and therefore define complicated UTI:

- Presence of catheter
- 100 mL of residual urine after voiding (neurogenic bladder)
- Obstructive uropathy (nephrolithiasis, fibrosis)
- Azotemia due to intrinsic renal disease
- Urinary retention in men, possibly due to benign prostatic hypertrophy

The signs and symptoms of complicated urinary tract infections are similar to those seen in acute pyelonephritis.

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*Pyelonephritis* is defined as a systemic, ascending urinary tract infection, clinically manifested by fever, chills, flank pain, nausea and/or vomiting, frequently associated with bacteremia due to the same pathogen as isolated in the urine. Symptoms of lower urinary tract infection may or may not be present.

### 3. Pathogens

In the majority of cases, complicated urinary tract infections and pyelonephritis are caused by pathogens from the enterobacteriaceae. Other etiologic agents include enterococci and *Pseudomonas* spp. The Agency does not consider coagulase-negative staphylococci or non-Group D streptococci as etiologic agents in patients with complicated UTI or pyelonephritis; these are generally considered to represent contamination.

## **C. Inclusion Criteria**

1. Clinical signs and symptoms should be present of an ascending UTI manifested by all three: fever, chills, and flank pain. In addition, patients may also have costo-vertebral angle tenderness, nausea, and/or vomiting.
2. Complicated UTI may also be characterized by lower urinary tract symptoms in patients with the following underlying conditions:
  - Indwelling catheter
  - 100 mL of residual urine after voiding
  - Neurogenic bladder
  - Obstructive uropathy due to nephrolithiasis, tumor, or fibrosis
  - Azotemia due to intrinsic renal disease,
  - Urinary retention in men possibly due to benign prostatic hypertrophy
3. One positive pretreatment clean catch midstream urine culture defined as  $\geq 10^5$  CFU/mL for the causative pathogen should be taken. If more than one pathogen is identified, each should be present at a colony count of as  $\geq 10^5$  CFU/mL to be included in the analysis. Urine samples should not be obtained from Foley bags.
4. In-vitro susceptibility testing of the uropathogen to both test and control drug should be undertaken.

## **D. Exclusion Criteria**

In addition to the general exclusion criteria, patients with the following conditions should be

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excluded:

- Prostatitis
- Intractable infection that requires >14 days of therapy
- Treatment with another antimicrobial within 48 hours or within 24 hours if only a single dose and in the presence of an appropriate positive culture
- Uncomplicated UTI
- Renal transplantation
- Ileal loops or vesico-ureteral reflux

### **E. Drugs and Dosing Regimens**

Standard treatment duration may range from a minimum of 7 days to a maximum of 14 days depending on the drug regimen. The control regimen should be approved for the treatment of complicated UTI or pyelonephritis. Use of unapproved control regimens should be discussed with the reviewing division. Consideration should be given to the transition from an intravenous to an oral route of administration during the course of therapy and dependent upon a determination of clinical response at predetermined time points.

### **F. Evaluation**

#### 1. Entry Visit

The pretherapy or baseline visit should be performed within the 2 days before starting treatment. This visit should include an assessment of the patient's history, a physical examination, vital signs, a pregnancy test when appropriate, a quantitative urine culture and sensitivity, a urinalysis, and serum chemistry and hematology. The compatibility with the inclusion and exclusion criteria should be assessed and an informed consent obtained. Randomization is permitted prior to the availability of the culture report. However, if the patient has not improved in the face of a negative culture or a resistant pathogen, the continuation of the study drug should be at the discretion of the investigator. If a patient is removed from the study for this reason, they are considered a failure.

#### 2. On-Therapy Visit

The on-therapy visit is optional and usually performed during study days 3 to 7. This visit can coincide with the conversion of a patient from parenteral to oral therapy, usually after the patient has been afebrile for 48 hours. Vital signs may be obtained and an assessment of clinical efficacy made at this visit. A urinalysis and culture also may be obtained and adverse events assessed.

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### 3. End-of-Treatment Visit

This visit is optional but should not be used to replace the test-of-cure visit.

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

The post-therapy visit at 5 to 9 days after the completion of treatment is considered the test-of-cure visit. This visit should include an assessment of clinical efficacy, determined by the physical exam as well as bacteriologic efficacy, determined by a urine culture and urinalysis. The patient should be assessed for adverse events and serum chemistry and hematology profiles obtained.

### 5. Late Post-Treatment Visit

The late post-therapy visit should be performed 4 to 6 weeks after the completion of therapy. The purpose of this visit is to assess relapse and recurrence rates in patients with complicated UTI or pyelonephritis. A clinical and microbiological assessment should be made. Laboratory safety studies do not routinely need to be repeated unless abnormalities were observed at the test-of-cure visit or unless warranted by the patient's condition. Absence of this visit would not make a patient unevaluable for efficacy analysis.

## **G. Outcome**

### 1. Clinical Outcome

The patient should have clinical signs and symptoms of a complicated urinary tract infection or pyelonephritis as listed above, meet the inclusion and exclusion criteria, have complied with the dosing regimen, and return 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



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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.

*Note:* The division recommends that *catheterized patients* have blood cultures (two sets from different sites) obtained simultaneously with the catheterized urine specimen at the time of study enrollment. (The urine sample should be obtained from the catheter using sterile technique — not from the Foley bag.) If two or more pathogens grow from the baseline urine culture, all isolates will be considered contaminants (i.e., unevaluable), unless the same pathogen is also isolated from a simultaneously obtained blood culture. If the same pathogen grows in the urine at  $\geq 10^5$  and is isolated from the blood, then it will be considered in evaluable pathogen.

### 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:

#### a. Clinical

*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.

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### b. Microbiological

*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.

## **H. Statistical Considerations**

The main analysis in studies of urinary tract infections or pyelonephritis should be based on patients with 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 is present in the urine, 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.

Patients with complicated urinary tract infections should be analyzed, and those with pyelonephritis should be analyzed as a subset. If the efficacy outcome in the two subsets are comparable, the results may be combined. If there is a major discrepancy in outcome between the two subsets, this should be explained.

Each study should be adequately powered to demonstrate therapeutic equivalence (using a 95% CI around the difference in therapeutic cure rates) of the test drug to the comparator for the per protocol evaluable population. The lower limit of the CI around the difference should not exceed -15% and the upper bound should include 0.

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**I. Review Issues**

(See also *General Considerations*.)

A complete presentation of the microbiology data is necessary, 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 should reflect the indication and organisms for which adequate data were presented. If adequate numbers of patients with complicated UTI and pyelonephritis are evaluated, both entities may be included in the labeling. 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.