Complicated Urinary Tract Infections: Developing Drugs for Treatment

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2015
Clinical/Antimicrobial

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Complicated Urinary Tract Infections: Developing Drugs for Treatment Guidance for Industry[1]

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I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment of complicated urinary tract infections (cUTIs).[2] Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs for drugs to support an indication for the treatment of cUTIs.

We consider the treatment of cUTIs to be an indication distinct from the treatment of uncomplicated urinary tract infections. This guidance addresses cUTI only. Sponsors interested in pursuing an indication for the treatment of uncomplicated urinary tract infections should discuss clinical development plans with the FDA.

This guidance does not contain discussion of the general issues of statistical analysis or clinical trial design. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[3]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the Division of Anti-Infective Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Complicated urinary tract infections are defined as a clinical syndrome characterized by pyuria and a documented microbial pathogen on culture of urine or blood, accompanied by local and systemic signs and symptoms, including fever (i.e., oral or tympanic temperature greater than 38 degrees Celsius), chills, malaise, flank pain, back pain, and/or costo-vertebral angle pain or tenderness, that occur in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization. Patients with pyelonephritis, regardless of underlying abnormalities of the urinary tract, are considered a subset of patients with cUTIs. Usually, one or more of the following conditions that increase the risk of developing a cUTI are present:

- Indwelling urinary catheter
- 100 milliliters (mL) or more of residual urine after voiding (neurogenic bladder)
- Obstructive uropathy (nephrolithiasis, fibrosis)
- Azotemia caused by intrinsic renal disease
- Urinary retention, including retention caused by benign prostatic hypertrophy

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Drug Development Population

The intended clinical trial population should be patients with all types of cUTIs. Because pyelonephritis is an important subset of cUTI, approximately 30 percent or more of the clinical trial population should be patients with pyelonephritis for an indication for "treatment of complicated urinary tract infections including pyelonephritis."

2. Efficacy Considerations

Noninferiority trials are interpretable and acceptable for the indication of treatment of cUTI. A showing of superiority is also readily interpretable.

A single adequate and well-controlled trial supported by other independent evidence, such as a trial in another infectious disease indication, can provide evidence of effectiveness.[4] Sponsors should discuss with the FDA the other independent evidence that would be used to support the findings from a single trial in cUTI.

[4] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

3. Safety Considerations

In general, we recommend a preapproval safety database of 700 patients or more. If the same dose and duration of therapy for treatment of cUTI were used in clinical trials for other infectious disease indications, the safety information from those clinical trials can be part of the overall preapproval safety database. For new drugs that have an important clinical benefit compared to existing therapies, a smaller preapproval safety database may be appropriate. Sponsors should discuss the appropriate size of the preapproval safety database with the FDA during clinical development.

4. Pharmacokinetic/Pharmacodynamic Considerations

The pharmacokinetic/pharmacodynamic (PK/PD) characteristics of the drug should be evaluated using in vitro models or animal models of infection, if not previously performed. Achieving adequate urine drug concentrations to evaluate antibacterial activity in the urine is an important consideration in patients with cUTI. Serum concentration of the drug is also an important consideration because patients with cUTI can have bacteremia and renal parenchymal involvement. The PK/PD characteristics of the drug can be used to guide selection of the dose and dosing interval based on serum and urine concentrations in relation to the minimum inhibitory concentration. Because concentrations can be influenced by renal impairment, sponsors should evaluate the effect of renal impairment on serum and urine concentrations early in clinical development. We recommend that blood and urine drug concentrations be evaluated in phase 1 and phase 2.

The PK/PD characteristics of the drug (including the relationships to the minimum inhibitory concentrations noted above) should be integrated with the findings from phase 1 PK clinical trials to help identify appropriate dosing regimens for evaluation in phase 2 and phase 3 clinical trials. A dose-response trial design can be considered as an option for clinical trials early in development to weigh the benefits and risks of various doses and to ensure that suboptimal doses or excessive doses (beyond those that add to efficacy) are not used in a phase 3 trial.

Collection of PK data in phase 2 clinical trials can be used to explore the exposure-response relationships and to confirm that the proper doses and regimens are selected for further evaluation in phase 3 clinical trials. Collection of PK data in phase 3 clinical trials may help to explain potential questions regarding efficacy or safety that might arise from the clinical trials. Sponsors should consider a sparse sampling strategy to include all patients in clinical trials with cUTIs to allow for the estimation of drug exposure in each patient.

B. Specific Efficacy Trial Considerations

1. Clinical Trial Designs, Populations, and Enrollment Criteria

Sponsors should conduct randomized, double-blind, and active-controlled cUTI trials, using a noninferiority or superiority design. Placebo-controlled trials are not appropriate for this indication except when they are add-on superiority trials in which patients receive either placebo or investigational drug added to standard-of-care antibacterial drug treatment.

The patient population should include patients with cUTI, and at least 30 percent of the patient population should have pyelonephritis for the indication for treatment of cUTI and pyelonephritis.

We recommend the following inclusion and exclusion criteria:

- **Recommended inclusion criteria:**
  - At least two of the following signs or symptoms:
    - Chills or rigors or *warmth* associated with fever (e.g., oral temperature greater than 38 degrees Celsius)
    - Flank pain (pyelonephritis) or pelvic pain (cUTI)
    - Nausea or vomiting
    - Dysuria, urinary frequency, or urinary urgency
    - Costo-vertebral angle tenderness on physical examination

  and

  - Urine specimen with evidence of pyuria:
    - Dipstick analysis positive for leukocyte esterase

      or

    - At least 10 white blood cells per cubic millimeter
- **Recommended exclusion criteria:**
  - Receipt of effective antibacterial drug therapy for cUTI for a continuous duration of more than 24 hours during the previous 72 hours[5]
  - Concurrent use of nonstudy antibacterial drug therapy that would have a potential effect on outcome evaluations in patients with cUTI
  - Patients with suspected or confirmed prostatitis
  - Patients with renal transplantation

[5] Patients who have objective documentation of clinical progression of cUTI while on antibacterial drug therapy, or patients who received antibacterial drugs for surgical prophylaxis and then develop cUTI, may be appropriate for enrollment.

- Patients with ileal loops

- Patients who are likely to receive ongoing antibacterial drug prophylaxis after treatment of cUTI (e.g., patients with vesico-ureteral reflux)

- Any recent history of trauma to the pelvis or urinary tract

- Patients with uncomplicated urinary tract infections (generally female patients with urinary frequency, urgency, or pain or discomfort without systemic symptoms or signs of infection)

2. Clinical Microbiology Considerations

Before receipt of clinical trial drug therapy, all patients should submit a urine specimen for culture and in vitro antimicrobial susceptibility testing.[6] Patients with an indwelling catheter should have urine samples collected following the placement of a new catheter, or aseptic techniques through a properly disinfected collection port if the indwelling catheter cannot be removed.

A microscopic evaluation (e.g., Gram stain) or dipstick analysis for leukocytes, nitrates, or a catalase test of the urine specimen should be performed. The urine specimen should be cultured by following established standard microbiology laboratory procedures. Sponsors should describe the urine collection and culture methods, and provide a standardized algorithm in the clinical trial site microbiology laboratories for final reporting of the culture results. In general, a single species of bacteria on pure culture identified at 10^5 colony forming units per milliliter (CFU/mL) or greater should be considered a true bacterial pathogen,[7] and no growth of bacteria (or growth at a quantitation of less than 10^4 CFU/mL) should be considered a microbiological success for a mid-stream clean-catch urine specimen (see section III.B.8., Efficacy Endpoints). In vitro antimicrobial susceptibility testing of the isolates to the investigational drug and to other recommended antimicrobial drugs that may be used to treat cUTIs should be performed using standardized methods unless otherwise justified.[8]

If there is growth of bacteria at a quantitation of less than 10^4 CFU/mL on a test-of-cure urine culture (e.g., fewer than 10 colonies of bacterial growth found on a quantitative urine culture using a 0.001 mL standard loop), the bacteria and in vitro antibacterial susceptibility should be evaluated. This additional evaluation is recommended in clinical trials of an investigational antibacterial drug to help understand the potential for antibacterial resistance. Even if the result

[6] Proper methods of urine specimen collection for analysis and culture are important enrollment considerations for clinical trials; see, for example, publications from the American Society for Microbiology, such as American Society for Microbiology, 2010, Clinical Microbiology Procedures Handbook, 3rd Edition, or a more recent edition; and American Society for Microbiology, 2009, Cumitech 2C: Laboratory Diagnosis of Urinary Tract Infections, coordinating editor SE Sharp, or a more recent edition.

[7] Sponsors should prespecify in the protocol how patients who have more than one bacterial species (isolated on a baseline urine culture) will be handled in the efficacy analysis.

[8] Standard methods for in vitro susceptibility testing are developed by organizations such as the Clinical and Laboratory Standards Institute, Wayne, PA.

of the test-of-cure culture is interpreted as urethral colonizing bacteria using a standard microbiology laboratory procedure (i.e., fewer than 10^4 CFU/mL on a clean catch mid-stream urine specimen), it would be important to identify cases in which the urethral colonizing bacteria developed resistance to the investigational drug.

We recommend blood cultures taken at two separate sterile venipuncture sites before initiation of clinical trial drug therapy.

All isolated bacteria considered to be possible pathogens should be saved in the event that additional testing of an isolate is needed (e.g., determination of genetic relatedness among strains by pulse-field gel electrophoresis or other molecular fingerprinting methods).

Development of new rapid diagnostic tests may facilitate future clinical trial design and potentially benefit patients by providing earlier diagnosis of causative organisms. Clinical trials of a new antibacterial drug for treatment of cUTI may provide an opportunity to contribute to the evaluation of a new diagnostic test. Sponsors interested in the development of a new rapid diagnostic test should discuss this opportunity with the FDA.

3. Randomization and Blinding

Patients should be randomized at enrollment to the treatments studied in the trial. All trials should be multicenter and double-blinded unless there is a compelling reason for single-blind or open-label trials. If trials are single-blind or open-label, sponsors should discuss potential biases with the FDA and how these biases will be addressed.

4. Specific Populations

The trials should include patients of both sexes and all races, as well as geriatric patients.[9] Patients with renal or hepatic impairment can be enrolled, provided the pharmacokinetics of the drug have been evaluated in these patients and appropriate dosing regimens have been defined.

Sponsors are encouraged to begin discussions about their pediatric clinical development plan as early as is feasible because pediatric studies are a required part of the overall drug development program and sponsors are required to submit pediatric study plans no later than 60 days after an end-of-phase 2 meeting or such other time as may be agreed upon by the FDA and the sponsor.[10]

In general, safe and effective treatments are available for pregnant patients with cUTIs. Therefore, it is generally appropriate to complete phase 3 clinical trials that establish safety and efficacy in nonpregnant patients before trials in pregnant patients are initiated. However, if treatment options are not available for pregnant patients with cUTIs (e.g., pregnant patients with

[9] See the ICH guidances for industry *E7 Studies in Support of Special Populations: Geriatrics* and *E7 Studies in Support of Special Populations: Geriatrics; Questions and Answers*.

[10] See the Pediatric Research Equity Act (Public Law 108-155; section 505B of the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. 355c), as amended by the Food and Drug Administration Safety and Innovation Act of 2012 (Public Law 112-144), and the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*. When final, this guidance will represent the FDA's current thinking on this topic.

bacterial pathogens resistant to all available antibacterial drugs), it may be appropriate to characterize safety and pharmacokinetics in pregnant patients with cUTIs who have the potential to benefit from the investigational drug. Before sponsors consider clinical evaluations of an investigational drug in pregnant women, they should complete nonclinical toxicology studies, reproductive toxicology studies, and phase 1 and phase 2 clinical trials. Infants born to mothers who received the investigational drug should be followed by the trial's investigators until at least 12 months of age.

5. Dose Selection and Formulations

To choose the dose or doses to be evaluated in phase 3 clinical trials, sponsors should integrate the findings from nonclinical toxicology studies, other in vitro animal studies, animal models of infection, pharmacokinetics, safety and tolerability information from phase 1 clinical trials, and safety and efficacy information from phase 2 dose-ranging clinical trials. An assessment of tissue penetration from animal studies as well as sufficient blood and urine concentrations in phase 1 and phase 2 trials can be used as supportive evidence that the selected dose is likely to achieve drug concentrations sufficient to exert an antimicrobial and clinical effect (see section III.A.4., Pharmacokinetic/Pharmacodynamic Considerations). In addition, pharmacokinetics of the drug in specific populations (e.g., patients with hepatic impairment) should be evaluated before initiation of phase 3 trials to determine whether dose adjustments are necessary. This evaluation may help avoid the exclusion of such patients from phase 3 clinical trials.

Antibacterial drug therapy for cUTI is generally initiated with an intravenous (IV) drug administered for several days followed by a switch to an oral drug to complete an overall course of antibacterial drug therapy for at least 7 days. For drugs that have both an IV and oral formulation, patients can switch from IV to oral drug during the trial provided that the pharmacokinetics of the IV and oral formulations have been adequately evaluated to determine appropriate dosing regimens.

For drugs that have only an IV formulation, the switch from the IV investigational drug to a different oral drug should allow enough time for proper assessment of the IV drug's safety and efficacy for treatment of cUTI (e.g., IV investigational drug for 5 days followed by a different oral antibacterial drug for 2 days to complete an overall course of treatment for 7 days). Approximately 5 days of IV therapy (i.e., 4 to 6 days of therapy) is generally recommended for this assessment and should be specified in the protocol. This time period is supported by recently conducted trials that defined a switch from IV to oral therapy (see the Appendix). The duration of the oral drug therapy, to complete at least a 7-day course of antibacterial drug therapy, also should be specified in the protocol.

6. Choice of Comparators

In general, the active comparator to be used in clinical trials should be one that is considered standard of care in the United States for this indication. When evaluating the current standard of care, we consider recommendations by authoritative scientific bodies (e.g., Infectious Diseases Society of America) based on clinical evidence and other reliable information that reflects current clinical practice.

7. Prior Nontrial Antibacterial Drug Therapy

Ideally, patients enrolled in a cUTI clinical trial should not have received prior antibacterial drug therapy because such therapy may obscure true treatment differences between an investigational drug and the control drug, thereby introducing bias toward a finding of no difference between treatment groups (i.e., a bias toward noninferiority). However, exclusion of all patients who have received prior antibacterial therapy could result in a patient population with lesser severity of illness and greater potential for spontaneous recovery; this also could bias trial results toward a finding of no difference between treatment groups (i.e., a bias toward noninferiority).

A pragmatic approach to these concerns is to: (1) encourage prompt enrollment procedures so that patients can receive the clinical trial treatment initially, with no need for other antibacterial drug therapy; and (2) allow enrollment of some patients who have received up to 24 hours of antibacterial drug therapy (ideally there would be few such patients but up to approximately 25 percent of the patient population may be appropriate). This would permit patients in the trial to receive prompt antibacterial drug therapy as clinically necessary, consistent with the standard of care. The total duration of the prior effective therapy should be less than 24 hours and ideally limited to one dose of an antibacterial drug with a short half-life. It would be important to evaluate the results in the subgroup of patients (i.e., the majority of patients) who did not receive prior effective antibacterial drug therapy.

8. Efficacy Endpoints

The following subsections describe the recommended primary efficacy endpoint and secondary endpoints.

a. Primary efficacy endpoint

The primary efficacy endpoint should be a responder outcome.

- **Clinical and microbiologic response:** Resolution of the symptoms of cUTI present at trial entry (and no new symptoms) and the demonstration that the bacterial pathogen found at trial entry is reduced to fewer than 10^4 CFU/mL on urine culture (microbiological success).[11]

- **Clinical or microbiologic failure:** Symptoms of cUTI present at trial entry have not resolved or new symptoms have developed, the patient has died, or the urine culture taken at any time during or after completion of therapy grows greater than or equal to 10^4 CFU/mL of the original pathogen identified at trial entry.

[11] Microbiological success is an important component of the responder endpoint because the ascending route of infection is the most common pathophysiological mechanism for cUTI. Continued bacteriuria at greater than 10^4 CFU/mL in patients recently completing treatment for cUTI represents a known risk for enhanced rate of relapse of cUTIs. Hence, microbiological success, along with resolution of symptoms, is the evidence needed to support a conclusion of treatment benefit (i.e., how a patient feels, functions, and survives). (See, for example, JD Sobel and D Kaye, 2010, Urinary Tract Infections, in GL Mandel, JE Bennett, R Dolin, eds., Principles and Practice of Infectious Diseases, 7th edition, Philadelphia, PA, Churchill Livingstone Elsevier, 957-985.)

In general, the efficacy evaluation (test of cure) for an investigational drug administered for the entire duration of therapy for cUTI should occur at a fixed time point after randomization. The fixed time point should include a period of observation after the completion of antibacterial drug therapy; the period of observation should be at least 5 days.[12] Symptom resolution should include all the core symptoms of cUTI (i.e., resolution of dysuria, urinary frequency, urinary urgency, suprapubic pain, and flank pain). Baseline symptoms associated with anatomic abnormalities that predispose to cUTI (e.g., symptoms associated with the presence of an indwelling urinary catheter) do not need to be resolved for a consideration of successful responder.

For an investigational drug that has only an IV formulation, the IV investigational drug should be maintained for approximately 5 days (i.e., 4 to 6 days of IV therapy) before a switch to an oral drug to provide a proper assessment of safety and efficacy of the IV drug. In addition to the primary efficacy endpoint at approximately day 5 of IV therapy, the maintenance of resolution of the core symptoms of cUTI and microbiological success at a fixed time point after randomization should be evaluated. For example, a trial in which patients receive 5 days of IV investigational drug therapy plus 2 days of oral therapy with another drug (for a total of 7 days of antibacterial drug therapy) should evaluate the responder outcome at approximately 14 days after randomization, allowing for a period of observation of approximately 7 days after completion of therapy. An IV investigational drug should demonstrate successful noninferiority (or superiority) at both endpoints: (1) at approximately day 5 of IV therapy as the primary efficacy endpoint; and (2) at a fixed time point after randomization that accounts for the total duration of antibacterial therapy plus a period of observation after completion of antibacterial drug therapy.

A symptom outcome assessment should use a structured assessment of responses given by the patient.[13] Sponsors should specify the methods that patients will use to record the core symptoms of cUTI for discussion with the FDA. The patient's assessment tool should include each of the core symptoms of cUTI at baseline and at the trial endpoint and should be noncomparative (i.e., it should not require patients to compare their current state with an earlier period).

b. Secondary endpoints

Patients should be evaluated for continued resolution of symptoms and microbiological success at a fixed time point approximately 21 to 28 days following randomization. This assessment helps to evaluate sustained microbiological success *and* resolution of all clinical symptoms of cUTI (a responder outcome) as a secondary endpoint. Sponsors also should evaluate the clinical outcome responses and microbiologic outcome responses separately at each fixed time point assessment as secondary endpoints.

[12] The period of observation after completion of antibacterial drug therapy depends on the PK characteristics and half-life of the drug, but in general should be a fixed time point specified in the protocol.

[13] See the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

9. Trial Procedures and Timing of Assessments

a. Entry visit

Sponsors should collect baseline demographic and clinical information at the entry visit and include clinical signs and symptoms, microbiologic specimens (Gram stain and culture of urine; blood culture), and laboratory tests, as appropriate.

b. On-therapy and end-of-therapy visits

Patients should be evaluated at least once during therapy or at the end of prescribed therapy. Clinical and laboratory assessments for safety should be performed as appropriate. If it is possible that the investigational drug would need to be continued beyond the protocol-specified duration, objective criteria for extending the therapy should be prespecified in the protocol. An on-therapy visit at the time of IV-to-oral switch should have a urine specimen obtained for microscopic examination and culture as well as clinical observations and patient symptoms.

c. Post-treatment visits

The responder endpoint should be evaluated at a fixed time point following randomization that accounts for the total duration of antibacterial drug therapy plus a period of observation of at least 5 days after completion of antibacterial drug therapy (e.g., a fixed time point at 14 days after randomization). Patients should be evaluated by history and physical examination for clinical signs, including vital signs, at this visit. Patients should be assessed at this visit for symptom resolution and a urine specimen should be obtained for microscopic examination and culture. An assessment for the maintenance of clinical response should occur at approximately 21 to 28 days after randomization.

10. Statistical Considerations

In general, sponsors should provide a detailed statistical analysis plan stating the trial hypotheses and the analysis methods before trial initiation. The primary efficacy analysis is usually based on the difference in the proportions of patients achieving a successful clinical and microbiological response.

a. Analysis populations

The following definitions apply to various analysis populations in cUTI clinical trials:

- **Intent-to-treat (ITT) population:** All patients who were randomized.

- **The microbiological intent-to-treat population (micro-ITT population):** All randomized patients who have a baseline bacterial pathogen on culture of urine or blood that causes cUTI against which the investigational drug and control drug have antibacterial activity. Patients should not be excluded from this population based upon events that occurred post-randomization (e.g., loss to follow-up).

- **Clinically evaluable or per-protocol populations:** Patients who meet the definition for the ITT population and who follow important components of the trial as specified in the protocol.

- **Microbiologically evaluable populations:** Patients who meet the definition for the micro-ITT population and who follow important components of the trial as specified in the protocol.

- **Safety population:** All patients who received at least one dose of drug during the trial.

The micro-ITT population should be considered the primary analysis population. Consistency of the results should be evaluated in all populations and any inconsistencies in the results of these analyses should be explored and explanations provided in the final report.

b. Noninferiority margins

Noninferiority trials can be an appropriate trial design if there is reliable and reproducible evidence of a treatment effect for the comparator drug.[14] For a cUTI trial, a noninferiority margin of 10 percent is supported by the historical evidence (see the Appendix). Sponsors should discuss with the FDA the selection of a proposed margin greater than 10 percent.

c. Sample size

An estimate of the sample size for a noninferiority trial with 1:1 randomization is approximately 425 patients per group based on a noninferiority margin of 10 percent and a clinical success rate in the micro-ITT population of 80 percent in the control group. Approximately 80 percent of patients should have a bacterial pathogen identified by culture (the micro-ITT primary efficacy analysis population would consist of approximately 337 patients per group). The trial should have enough statistical power to rule out a greater than 10 percent inferiority of the investigational drug to control drug (upper bound of the two-sided 95 percent confidence interval for the clinical success rate of control drug minus investigational drug).

C. Other Considerations

1. Relevant Nonclinical Considerations

New antibacterial drugs being studied for cUTIs should have nonclinical data documenting activity against commonly implicated pathogens for cUTI.[15] Animal models of cUTIs may contribute to demonstrating proof of concept for the treatment of cUTIs and for evaluating antibacterial activity. Animal studies should not be considered a substitute for clinical trials in

[14] See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic.

[15] See the draft guidance for industry *Microbiological Data for Systemic Antibacterial Drug Products — Development, Analysis, and Presentation*. When final, this guidance will represent the FDA's current thinking on this topic.

patients with cUTIs that must be conducted to evaluate safety and efficacy of the drug (21 CFR 314.600).

2. Labeling Considerations

The labeled indication under the INDICATIONS AND USAGE section should reflect the patient population enrolled in the clinical trials. Approximately 30 percent of the patient population in the cUTI clinical trials should have a diagnosis of pyelonephritis for the indication to include treatment of both complicated urinary tract infections and pyelonephritis.

APPENDIX: JUSTIFICATION FOR NONINFERIORITY MARGIN FOR COMPLICATED URINARY TRACT INFECTIONS

A literature search found four articles published before the availability of antibacterial drug therapy that are case series of patients in which the clinical courses of patients with cUTIs, in the absence of antibacterial drug treatment, were described.

A total of seven recently conducted clinical trials were identified that evaluated drugs approved for treatment of cUTI that had sufficient data to assess clinical and microbiologic outcomes of individual patients after a period of observation following completion of antibacterial drug treatment (end of all therapy). Four of the seven clinical trials that evaluated IV antibacterial drugs included an oral switch and had sufficient data to assess outcomes on individual patients at the time of the IV-to-oral switch (end of IV therapy).

Case Series of Patients With cUTI Before the Availability of Antibacterial Drugs

The results of the four case series that describe the natural history of cUTIs without the use of antibacterial drugs are shown in Table 1. One article described the responder endpoint, while three articles described either microbiological success or clinical response. We chose to consider *microbiological success + clinical response* as representing the greatest proportion that could have achieved both microbiological success and resolution of clinical symptoms. Overall clinical and microbiological success in these pre-antibacterial studies was no higher than 30 percent. As noted in Table 1, an upper bound for meta-analysis of the results is about 33 percent.

Table 1. Summary of Studies of cUTI Before Antibacterial Drug Therapies

Study	Population	Timing of Evaluation	Microbiological Success	Clinical Response	Microbiological Success + Clinical Response	Endpoint Specified in the Paper
Culver 1918[1,2,3]	Adults with cUTI	83% completed the nonantibacterial therapy within 1 month	Not provided	Not provided	30/116 (25.9%)	Relief of symptoms and two successive *negative* cultures
Henline 1925[3,4]	Adults with cUTI	Nonantibacterial therapy administered until negative cultures	7/31 (22.6%)	Not provided	Not provided ≤ 7/31 (22.6%)	*Negative* urine cultures obtained by cystoscopy
Koll 1911[3,5]	Adults with cUTI	Nonantibacterial therapy administered until sterile urine obtained	4/15 (26.7%)	Not provided	Not provided ≤ 4/15 (26.7%)	*Sterile* urine cultures
Todd 1857[6,7]	Adults with cUTI	Supportive therapy or surgical intervention	Not provided	3/10 (30%)	Not provided ≤ 3/10 (30.0%)	Not specified, in general relief of symptoms
DerSimonian and Laird random effects meta-analysis for the microbiological success + clinical response: 25.6% (95% CI: 19.6%, 32.7%)[8]						

[1] Culver, H, RD Herrold, and FM Phifer, 1918, Renal Infections: A Clinical and Bacteriologic Study, Journal of the American Medical Association, 70:1444-1448.
[2] This paper provides the best estimate of an endpoint of both clinical and microbiological cure for patients with cUTI treated without antibacterial drug therapy.
[3] Therapies at this time consisted of altering the urinary pH or altering surface tension that may have resulted in an indirect antibacterial effect. Patients had symptoms of cUTI for months or in some cases years before presenting for treatment.
[4] Henline, RB, 1925, Hexyl Resorcinol in the Treatment of 50 Cases of Infections of the Urinary Tract, J Urol, 14:119-133.
[5] Koll, IS, 1911, An Experimental and Clinical Study of the Colon Bacillus Infections of the Urinary Tract, J Urol, VII(11):417-428.
[6] Todd, R, 1857, Clinical Lectures on Certain Diseases of the Urinary Organs and on Dropsies, Philadelphia: Blanchard and Lea, 243-261.
[7] Later in the 1800s, the germ theory of disease was described by Louis Pasteur and Robert Koch.
[8] DerSimonian, R and N Laird, 1986, Meta-Analysis in Clinical Trials, Control Clin Trials, 7:177-187.

Evaluation of Recently Conducted Phase 3 Trials of cUTI for End of Therapy

Table 2 includes the results of active-controlled trials of drugs approved for treatment of cUTI at the time of the trial or drugs subsequently approved for treatment of cUTI based on these successful trial results. The trials reported microbiological success and investigator-assessed clinical responses for individual patients at time points ranging between 3 to 10 days after completion of antibacterial drug therapy. In general, antibacterial drug therapy was administered for approximately 2 weeks. Microbiological success for all of these trials was defined as having fewer than 10^4 CFU/mL on quantitative urine cultures. Clinical response was defined, in

general, as complete resolution of symptoms or improvement in symptoms such that no additional antibacterial drugs were required. Some trials in Table 2 have two treatment groups and each group is displayed separately. The analyses are based on the micro-ITT population (i.e., all patients with a documented bacterial infection).

Table 2. Summary of Phase 3 Trials in Patients With cUTI; Micro-ITT Populations

Study	Day of Evaluation	Microbio-logical Success	Clinical Response	Microbiological Success + Clinical Response	Source
1	7-10 d post-Rx	171/208 (82.2%)	188/208 (90.4%)	164/208 (78.8%)	Trial datasets
2	7-10 d post-Rx	149/192 (77.6%)	166/192 (86.5%)	139/192 (72.4%)	Trial datasets
3	5-9 d post-Rx	197/227 (86.8%)	185/227 (81.5%)	180/227 (79.3%)	Trial datasets
	5-9 d post-Rx	209/248 (84.3%)	206/248 (83.1%)	197/248 (79.4%)	Trial datasets
4	5-9 d post-Rx	106/139 (76.3%)	112/139 (80.6%)	104/139 (74.8%)	Trial datasets
	5-9 d post-Rx	54/73 (74.0%)	55/73 (75.3%)	51/73 (69.9%)	Trial datasets
5	6-9 d post-Rx	257/325 (79.1%)	291/325 (90.0%)	241/325 (74.2%)	Trial datasets
	6-9 d post-Rx	253/323 (78.3%)	260/323 (80.5%)	233/323 (72.1%)	Trial datasets
6	6-9 d post-Rx	278/337 (82.5%)	294/337 (87.2%)	255/337 (75.7%)	Trial datasets
7	3-9 d post-Rx	240/317 (75.7%)	224/317 (70.7%)	201/317 (63.4%)	Trial datasets
	3-9 d post-Rx	229/302 (75.8%)	205/302 (67.9%)	193/302 (63.9%)	Trial datasets
DerSimonian and Laird random effects meta-analysis for the microbiological success + clinical response: 73.2% (95% CI: 69.6%, 76.6%) (See note 8 at the bottom of Table 1.)					

Overall, the rate of microbiologic and clinical success was not lower than 63 percent and the mean response in the meta-analysis was 73 percent with a lower bound of the 95 percent confidence interval at almost 70 percent.

Treatment Effect and Support for Noninferiority Margin for End of Therapy

An estimate of the treatment difference can be derived from comparing the upper bound of the rate of the microbiological success plus clinical resolution noted before antibacterial drug therapies were available (approximately 33 percent from Table 1), and the lower bound of the rate of the microbiological success plus clinical resolution from recently conducted clinical trials of antibacterial drugs (approximately 70 percent from Table 2). There is thus clear evidence of an effect of the active control (i.e., historical evidence of sensitivity to drug effect) and the treatment difference is estimated to be 37 percent (70 percent minus 33 percent). It may be reasonable to estimate the entire effect of the active control (M_1) at 37 percent, but given the

uncertainties with the data presented in the historical case series, the effect of the active control (M_1) should be somewhat discounted. Therefore, we choose M_1 of 30 percent.

For the selection of a noninferiority margin, a proportion of M_1 should be preserved to maintain the important treatment effects of antibacterial drugs in the treatment of cUTI. Thus, a noninferiority margin (M_2) of 10 percent can be supported for active-controlled clinical trials of cUTI using a responder endpoint of microbiological success plus clinical resolution at a fixed time point after randomization that accounts for the total duration of antibacterial drug therapy plus a period of observation of at least 5 days after completion of antibacterial drug therapy, in the patient population with microbiologically documented cUTI. Sponsors should discuss with the FDA the selection of a noninferiority margin greater than 10 percent.

Treatment Effect and Support for Noninferiority Margin for End of IV Therapy

We evaluated patient-level data from phase 3 IV-to-oral-switch trials in patients with cUTI that were submitted to support an application for approval of an IV drug. The trials provided specific clinical and microbiological criteria for switching from IV to oral therapy. In general, patients were required to have microbiological success on therapy and to have achieved improvement in clinical symptoms before switching to oral therapy. We considered clinical response as having complete resolution of symptoms of cUTI at the timing of the IV-to-oral switch (i.e., resolution of dysuria, frequency, suprapubic pain, urgency, and flank pain, which were evaluated in all trials). In addition, some trials also required that patients should not have nausea or vomiting upon switching to oral therapy. The information on resolution of nausea or vomiting was not recorded on case report forms and therefore was not used as a specific symptom response or resolution in the trials' electronic datasets. Table 3 provides a summary of the trials that incorporated an IV-to-oral switch and evaluated symptom responses at the timing of the IV-to-oral switch.

Table 3. Summary of Phase 3 Trials Evaluating Responses at End of IV Therapy

Study Group	Mean Duration of IV Therapy	Microbiological Success During Treatment With IV	Clinical Response at End of IV Therapy*	Microbiological Success + Clinical Response	Source
1	4.0 days	100%	106/216 (49.1%)	106/216 (49.1%)	Trial datasets
2	4.1 days	100%	113/230 (49.1%)	113/230 (49.1%)	Trial datasets
3	4.0 days	100%	87/130 (66.9%)	87/130 (66.9%)	Trial datasets
4	4.0 days	100%	47/67 (70.1%)	47/67 (70.1%)	Trial datasets
5	5.4 days	100%	230/317 (72.5%)	230/317 (72.5%)	Trial datasets
6	5.3 days	100%	224/311 (72.0%)	224/311 (72.0%)	Trial datasets
7	5.5 days	100%	230/329 (69.9%)	230/329 (69.9%)	Trial datasets
DerSimonian and Laird random effects meta-analysis for the microbiological success + clinical response: 64% (95% CI: 56%, 72%) (See note 8 at the bottom of Table 1.)					

* The five symptoms that were evaluated as having complete resolution in this analysis were symptoms evaluated among all seven study groups: dysuria, frequency, suprapubic pain, urgency, and flank pain.

Treatment Effect and Support for Noninferiority Margin for End of IV Therapy

An estimate of the treatment difference of an IV antibacterial drug can be derived from comparing the upper bound of the rate of microbiological success plus clinical response noted before antibacterial drug therapies were available (approximately 33 percent from Table 1), and the lower bound of the rate of microbiological success plus clinical response from recently conducted clinical trials of antibacterial drugs using the time point of a switch from IV to oral therapy (approximately 56 percent from Table 3). The treatment difference is estimated to be 23 percent (56 percent minus 33 percent). Given the uncertainties with the data presented in the historical case series, the effect of the active control (M_1) should be somewhat discounted. Therefore, we choose M_1 of 20 percent.

On clinical grounds, an M_2 of 10 percent can be supported for active-controlled clinical trials of cUTI using a responder endpoint of microbiological success plus clinical resolution at a fixed time point of approximately 5 days of IV investigational drug therapy at the time of IV-to-oral switch. Trials should continue to follow patients throughout the course of therapy and a period of observation of at least 5 days after completion of antibacterial drug therapy (e.g., a fixed time point at approximately 14 days after randomization) for overall evaluation of safety and efficacy of the IV investigational drug. Sponsors should discuss with the FDA the use of a noninferiority margin greater than 10 percent.