Guidance for Industry

Acute or Chronic Bacterial Prostatitis — 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DRAFT GUIDANCE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Additional copies of this draft guidance document are available from the Drug Information Branch, Division of Communications Management, HFD-210, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4573,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.

For questions on the content of the draft document contact Renata Albrecht, 301-827-2336.

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TABLE OF CONTENTS

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GUIDANCE FOR INDUSTRY[1]

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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 bacterial prostatitis.

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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[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 bacterial prostatitis. 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.

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.

The classification and categorization of the clinical entity of *prostatitis* has been fraught with diagnostic and management challenges. A review of current literature reveals that the preferred classification system identifies four clinical syndromes or subgroups of patients:

- Acute bacterial prostatitis
- Chronic bacterial prostatitis
- Nonbacterial prostatitis
- Prostadynia

It should be noted that the currently used classification system (Drach et al.) separates the four clinical entities of prostatitis by chronology, severity of symptoms, and the presence or absence of leukocytes and/or bacteria in the various segmented lower urinary tract cultures. However, this system has not been validated in adequate and well-controlled studies and in the opinion of many urologists has created great confusion in the field with respect to the diagnosis and treatment of prostatitis.

The NIH Consensus Conference on Prostatitis has proposed a new classification system. This system also divides prostatitis into four categories, which are listed and described below:

Category I:	Acute Bacterial Prostatitis = Acute infection of the prostate gland
Category II:	Chronic Bacterial Prostatitis = Recurrent infection of the prostate
Category III:	Chronic Abacterial Prostatitis/CPPS[3]: No demonstrable infection
Category IIIA:	Inflammatory CPPS = White cells in semen/EPS/VB3 or post-prostatic massage

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

[3] CPPS = Chronic Pelvic Pain Syndrome

Category IIIB: Noninflammatory CPPS = No white cells in semen/EPS/VB3

Category IV: Asymptomatic Inflammatory Prostatitis = No subjective symptoms detected either by prostate biopsy or by the presence of white cells in EPS/semen during evaluation for other disorders

It also should be noted that the NIH classification system has not been validated; however, its use is becoming increasingly prevalent. Furthermore, there is reasonable overlap in Categories I and II, or acute and chronic prostatitis, respectively, and the similarly named entities in the previous classification system. These entities are defined by the presence of uropathogenic bacteria cultured from specific prostatic specimens. This draft document provides guidance to industry on the development of antimicrobials for the treatment of these two bacterial syndromes. This document does not address the subgroups of nonbacterial inflammatory processes or CPPS.

The current IDSA guidance states that any UTI in a man > 40 years of age is to be associated with bacterial invasion of the prostate or kidney. Furthermore, the differentiation in most men between bacterial prostatitis and bacterial urinary tract infection (UTI) is artificial and inaccurate. The distinction should be eliminated for the purpose of clinical trials, and all UTIs in men should be considered *complicated*. Despite this, IDSA provides for a modified trial design and evaluability criteria for the entity of bacterial prostatitis. This guidance is consistent with that stance and reflects the need for a more prolonged duration of therapy, a more complex method of diagnostic testing, and clinical as well as microbiological documentation to be able to draw regulatory conclusions about drug's safety and efficacy.

It should be emphasized that the differentiation of prostatitis into acute or chronic disease is not only clinically driven, but also microbiologically driven. The issue of the differentiation has been dealt with by divisions within ODE IV within the last 2 to 3 years and has led to the recent approvals and labeling for chronic bacterial prostatitis as opposed to the previously used and more generic term of *bacterial prostatitis*.

III. ACUTE OR CHRONIC BACTERIAL PROSTATITIS

A. Regulatory Synonyms

A number of synonyms have been used in the past in discussions of this indication, and the Agency has approved several agents for the treatment of *bacterial prostatitis* and, more recently, *chronic bacterial prostatitis*.

B. Study Considerations

1. Study Characteristics

If effectiveness of the compound has already been established in complicated urinary tract infections, a statistically adequate and well-controlled multicenter trial is recommended establishing safety and effectiveness (i.e., similar or superior effectiveness to an approved product). For this infection, patients should be both clinically and microbiologically evaluable. Pathogens listed in the INDICATIONS AND USAGE section of the product labeling should be those as delineated below.

Some potential pathogens, such as species of *Chlamydia,* should be evaluated on their responses in this study and in investigations of treatment of other infectious sites involving *Chlamydia.*

Adequate microbiologic data and specific human pharmacokinetic/dynamic data supportive of clinical effectiveness in this disease entity should also be obtained. Such studies would include, but not be limited to, tissue distribution studies that demonstrate that the investigative agent diffuses into prostatic secretions and tissues in quantities adequate to achieve and maintain prostatic secretions and tissue levels of antimicrobial compound equal to or above the expected MIC_{90} of the claimed pathogens for an adequate time period.

2. Prostatitis Classification

As stated above, this document focuses on the evaluability criteria for bacterial prostatitis, both acute and chronic, and differentiates between the two where indicated.

3. Regarding Pathogens:

In the majority of cases of acute or chronic bacterial prostatitis, the causative pathogens are *Escherichia coli, Enterococcus faecalis,* and *Proteus mirabilis. Pseudomonas aeruginosa* is also seen occasionally. Other Gram-positive cocci are found less frequently. *Staphylococcus aureus* can cause an acute bacterial prostatitis in the face of catheter usage. Alternatively, coagulase-negative staphylococci, such as *Staphylococcus haemolyticus* or *Staphylococcus epidermidis*, can be considered pathogens, more commonly in chronic bacterial prostatitis of a recurrent nature.

In addition to the above, infections of the prostate may also occur with *Neisseria gonorrhoeae, Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma* spp., or, rarely, trichomonads. These latter organisms are seen more commonly in acute prostatitis

in patients less than 35 years old.

The isolation of coagulase-negative staphylococci will generally not be considered evidence of an etiologic pathogen. These are generally considered to represent contamination. For these agents to be considered etiologic, several conditions need to be met, as specified in the microbiology section of this guidance.

4. Disease Definitions

In *Urinary Tract Infections, Detection, Prevention, and Management* (1997) , Calvin Kunin describes *acute bacterial prostatitis* as a suppurative process characterized by fever, chills, leucocytosis, and acute perineal and low back pain, and in more severe cases, bacteremia, shock, and disseminated intravascular coagulation (DIC). Blood cultures are often positive with the same microorganism found in the urine. *Escherichia coli* and other uropathogens are considered to be the etiologic agents. *Chronic bacterial prostatitis* may be asymptomatic or characterized by a sensation of perineal fullness, low back pain, dysuria, and pyuria. Fever is not as common. The hallmark of the process is the presence of the same microorganism with each recurrent episode of UTI. This is the most important cause of recurrent UTI in the adult male. It is difficult to eradicate because of the presence of prostatic calculi. The microorganisms are the same uropathogens as found in UTIs. Coagulase-negative staphylococci, alpha-hemolytic streptococci, and diptheroids are part of the normal flora of the male urethra and only rarely cause infections.

Prostadynia is a noninflammatory condition of unknown origin, encountered most often in young men and characterized by a sense of fullness or pressure in the perineum, testicles, and low back. The EPS secretions are sterile.

Generally, submissions for this indication provide for subjects with the chronic form of this disease as opposed to the acute. The significance of this is the difficulty in obtaining appropriate bacteriologic specimens in patients suffering from true acute disease because of the possibility of the development of bacteremia during prostatic massage.

It is strongly recommended that documentation be provided with regard to the duration of the present episode, as well as the duration of the disease, so that an accurate assessment of the population under study can be made for labeling purposes (to differentiate between acute and chronic disease).

C. Inclusion Criteria

Adult and/or geriatric male patients should present the following conditions within 0 to 5 days of starting the study drug:

- A tender, tense prostate on rectal exam consistent with a diagnosis of acute prostatitis

  or

- A soft, tender prostate without nodules consistent with a diagnosis of chronic prostatitis

  and

- One or more symptoms from the following group: Disturbances of urination, including frequency, urgency, dysuria, and/or lower urinary tract obstruction (more commonly seen in patients with chronic disease), hesitancy, decreased stream, urinary retention; perineal or low back pain; fevers; or chills.

The clinical picture of either form of prostatitis can mimic the other. Patients with acute disease can have septicemia as well as fever.

The bacteriologic assessment for inclusion should include the evaluation of sequential urine cultures as described by Mears and Stamey. This technique includes the following four specimens:

- Voided bladder 1 (VB_1) — Initial 5-10 mL of urine specimen
- Voided bladder 2 (VB_2) — Clean-catch midstream urine specimen
- Expressed prostatic secretions (EPS) — Secretions expressed from prostate by digital massage after midstream urine specimen
- Voided bladder 3 (VB_3) — First 5-10 mL of urine stream immediately after prostatic massage

The diagnosis of acute or chronic bacterial prostatitis is confirmed by one of the following criteria:

- The colony count of a pathogen in VB3 *exceeds* that in VB_1 or VB_2 by 10 fold

- The colony count of a pathogen in EPS *exceeds* that in VB_1 or VB_2 by 10 fold.

In the face of a true acute prostatitis, it may be clinically contraindicated to perform a prostatic

massage. Thus, patients with a clinical diagnosis of acute prostatitis characterized by a swollen, exquisitely tender prostate as determined by rectal exam and with a VB_2 specimen growing $\geq 10^5$ CFU/mL of an accepted pathogen will be considered as having met the diagnostic inclusion criteria. Additionally, patients with acute disease should have a WBC count obtained and blood culture performed.

D. Exclusion Criteria

In addition to routine exclusion criteria, patients with the following conditions should be excluded because these conditions may interfere with the assessment of the study drug safety and efficacy.

- Known prostatic cancer
- Presence of any other infection at enrollment that may require treatment with an antibiotic other than the study drug
- Treatment with any systemic antibiotic for 24 hours or longer within seven days prior to entry into the study, unless there is documented evidence of resistance or clinical failure

If patients with a permanent transurethral catheter, a history of cystostomy or nephrostomy, or a history of transurethral resection of the prostate within six months of study enrollment are included in the study because they do have prostatitis based on the above-listed clinical and bacteriological criteria, their outcomes should be analyzed separately (subsets). It should be noted, however, that the clinical outcome and even the microbiological outcome in patients with these conditions may be difficult to evaluate or may be confounded by the underlying conditions. This limitation should therefore be taken into consideration when planning sample size, enrollment, randomization and analysis.

E. Drugs and Dosage Regimen

Treatment duration is dependent on the drugs to be tested and the treatment regimen. The comparator agent should be one that is approved for the treatment of bacterial prostatitis.

A patient should have received between 80% to 120% of the treatment regimen. However, patients who are considered as having an inadequate response to treatment after receiving approximately one week of study drug and patients whose study drug is changed to another antimicrobial agent should be classified as clinical failures.

1. Entry Visit

The baseline evaluation should be performed within 0 to 5 days prior to the entry visit —

the first day of the study. This baseline evaluation may coincide with the day of entry, randomization, and start of therapy in acutely ill patients. Alternatively, the evaluation and enrollment may be split into two visits, an initial pretherapy screening visit where the patient with an indolent chronic process is worked up to determine whether the etiology of his complaints is a chronic bacterial prostatitis, followed by an entry visit up to 5 days later to undergo randomization and start therapy. The rationale for the delay in starting therapy in patients with a more chronic form of prostatitis is to provide the ability to the sponsor to maximize the evaluable population by first screening them via physical exam and culture and subsequently randomizing and starting therapy.

The baseline visit should include an assessment of the patient's history, physical examination, vital signs, serum chemistry, and hematology, and confirmatory bacteriologic evaluation of sequential urine cultures as described above. The compatibility with the inclusion and exclusion criteria should be assessed and an informed consent obtained. The clinical and preferrably bacteriological diagnosis of bacterial prostatitis should be confirmed prior to the start of therapy. In the case where a culture results is obtained after the start of therapy and reveals no bacterial growth, the patient should be considered not evaluable for the efficacy evaluation. If the culture and susceptibility test results show that the patient has a resistant pathogen, the institution or continuation of the study drug should be at the discretion of the investigator and should be guided by the expected benefit to the patient and by the patient’s clinical course.

In the case of those patients where the baseline evaluation is divided into a pretherapy or screening visit and a second visit for randomization and start of therapy, the information obtained at the baseline evaluation, including identification of the etiological pathogen, should be recorded in the case record form. This information does not have to be duplicated at the time of randomization and start of therapy.

2. On-Therapy Visit

The on-therapy visit should take place during the first 3 to 10 days after the start of therapy and include an assessment of the patient’s clinical response to treatment. The wide time range has been provided to accommodate a mixed population of patients with varying degrees of severity of illness. Thus, for patients with acute bacterial prostatitis, an on-therapy visit within a few days of the start of therapy may be appropriate. Patients with chronic bacterial prostatitis may be more appropriately evaluated after at least one week of therapy. Instead of scheduling a clinical visit, the investigator may contact the patient by telephone and ask about the current status of the patient’s presenting signs and symptoms as well as about potential new signs and symptoms and adverse drug reactions. It answers to these questions reveal that the patient is not responding adequately or raise other concerns, the patient should be called in for an examination and reevaluation. A

patient who returns for a clinic visit should have a clinical reevaluation of the symptoms of bacterial prostatitis, including a rectal examination if indicated. An assessment for any new or evolving signs or symptoms since the baseline visit should be obtained in patients without clinical improvement. A routine urine culture may be obtained from a clean-catch midstream urine specimen. The results of this culture have no implications upon therapy unless the investigator determines that the subject's clinical condition warrants a change. Other assessments performed at this visit should include the recording of vital signs, concomitant medication, study drug dosing, adverse events volunteered by the subject or observed by the investigator, and laboratory (hematology, serum chemistry, and urinalysis) evaluations.

3. End-of-Therapy Visit

This is an optional visit but should not be used a substitute for the test-of-cure visit.

4. Post-Therapy, Test-of-Cure Visit

The first post-therapy visit should take place 5 to 9 days after the end of treatment. This visit is considered the test-of-cure visit. An efficacy evaluation, taking into account the clinical assessment of signs, including rectal prostate exam, and symptoms of bacterial prostatitis, as well as any new signs or symptoms since the previous visit, should be performed. The investigator should make a global clinical assessment, comparing to the screening assessment. Quantitative bacteriological culture, as outlined above, should be repeated. If expressed prostatic secretion (EPS) cannot be obtained after prostatic massage, bacteriological efficacy may be based on urine cultures from VB_1, VB_2, and VB_3.

In addition to the efficacy evaluation, other assessments include recording of vital signs, concomitant medication, study drug dosing, adverse events volunteered by the subject or observed by the investigator, and laboratory (hematology, serum chemistry, and urinalysis) evaluations.

5. Late Post-Therapy Visit

The final post-therapy visit should take place 4 to 6 weeks after the end of therapy and is used solely to assess for recurrence in those subjects cured at the test-of-cure visit. At this visit, an efficacy evaluation similar to those described above (including a manual examination of the prostate) should again be performed and a global clinical assessment made. Quantitative bacteriological cultures should be repeated as outlined above. Laboratory evaluations performed at previous visits should be repeated at this visit only if clinically significant results were detected at the test-of-cure visit.

It is recognized that an important aspect in the evaluation of prostatitis, and other infections, is the ability to quantitate symptoms. This quantitation enables the investigator to make a more objective or consistent assessment of outcome. Therefore, it is of value to use some form of a symptom assessment instrument to evaluate the efficacy of antimicrobials for this indication. Currently, no validated symptom scoring system or Agency endorsed scoring system is widely used. The following four available questionnaires are recommended:

- Neal and Moon: Symptom Score Questionnaire
- Krieger et al.: University of Washington Symptom Score
- Giessen Prostatitis Symptom Score (GPSS)
- Nickel at al.: Prostatitis Symptom Severity Index (SSI) and Symptom Frequency Questionnaire (SFQ)

F. Outcome

1. *Clinical Outcome*: Patients with a clinical diagnosis of bacterial prostatitis who meet all inclusion and exclusion criteria, comply with the treatment regimen, and return for the 5- to 9-day post-treatment visit.

    a. *Clinical Cure*: The resolution of all signs and symptoms at 5 to 9 days posttherapy and no use of additional antimicrobial therapy for the infection.

    b. *Clinical Failure*: No response to therapy, worsening of pretherapy signs and symptoms at 5 to 9 days post-therapy, or use of additional antimicrobial therapy for the treatment of the infection.

Patients who receive an additional antimicrobial for the treatment of prostatitis should be considered evaluable and classified as clinical failures. Once a patient has been considered to have failed therapy, the patient should be retained in the analysis even if documentation of subsequent visits is lacking. The category *improvement* has been omitted to provide for a dichotomous *cure/fail* analysis.

2. *Microbiological Outcome*: A patient who meets the clinical criteria and has a positive EPS and/or VB3 urine specimen at baseline and a follow up sequential urine culture at the 5- to 9-day visit.

    a. *Eradication*: A sequential culture obtained within the 5- to 9-day post-therapy window, that reveals that the pathogen isolated at entry has been eradicated from VB3 or EPS.

b. *Persistence*: A sequential culture obtained at or before the 5- to 9-day post-therapy visit that reveals continued growth of the original pathogen in the EPS or VB_3 specimen.

c. *Superinfection*: The isolation of a pathogen, other than the baseline pathogen in any on-therapy specimen, associated with worsening or emergence of clinical evidence of infection.

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

For subjects to be reevaluated at this visit, they should have been considered to have a clinical cure and microbiological eradication at the 5- to 9-day post-therapy visit. Patients who were considered to be clinical failures and/or have microbiological persistence should have this failure assessment carried forward as failures as outlined above.

a. Clinical Outcome

Sustained Cure: All pretherapy signs and symptoms remain resolved at the 4- to 6-week post-therapy visit in subjects classified as cures at the 5- to 9-day post-therapy visit.

Failure: All patients who were failures at the 5- to 9-day visit are carried forward.

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

Unevaluable: Any patient who receives another antimicrobial capable of eradicating a pathogen, during therapy or during the entire study period, will be considered unevaluable if, as stated above, that antimicrobial was prescribed for an unrelated disease process.

b. Microbiological Outcome

Sustained Eradication: A sequential culture obtained within the 4- to 6-week post-therapy window that reveals that the pathogen found at entry remains eradicated in the VB3 or EPS specimens.

Persistence: Same definition as persistence at 5 to 9 days, persistence is carried forward.

Recurrence: The isolation of the original pathogen at any time in the EPS or VB3

specimens after the documented eradication of this organism at the 5- to 9-day post-therapy or test-of-cure visit.

G. Statistical Considerations

The evaluation of bacterial prostatitis should be based on patients who meet both clinical and microbiological protocol criteria.