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May 24, 2012

Division of Dockets Management (HFA-305)  
U.S. Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

### **Re: Comments on Docket #FDA- 2012-D-0148; Draft Guidance for Industry on Complicated Urinary Tract Infections: Developing Drugs for Treatment; 77 Federal Register 11133; February 24, 2012**

Dear Sir/Madam:

The Infectious Diseases Society of America (IDSA) is pleased to submit comments on the above referenced Food and Drug Administration (FDA) Draft Guidance concerning complicated urinary tract infections (cUTI). IDSA represents nearly 10,000 infectious diseases physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative bacterial infections such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and, finally, emerging infections such as the 2009 H1N1 influenza virus and bacteria containing the New Delhi metallo-beta-lactamase (NDM-1) enzyme that makes them resistant to a broad range of antibacterial drugs.

For the past decade, IDSA has raised concerns about the imbalance between the dwindling antibiotic pipeline and the significant and concomitant need for new, safe and efficacious antibacterial drugs to treat an increasing number of serious and life-threatening drug-resistant infections. We greatly appreciate the effort the FDA has put into the new cUTI draft guidance. Since there is a tremendous public health need now for new agents to treat infections caused by Gram-negative bacilli (GNB), and GNB are the predominant pathogens in the cUTI setting, the availability of a feasible, clinically relevant clinical trial guidance in this area is of great importance.

There are favorable elements of the guidance, such as the use of clinical and microbiological endpoints, the emphasis on proper pharmacokinetic (PK) data to support the phase III trials, the safety section, and the mention of incorporation of rapid diagnostic testing. Other areas are of concern, as summarized in the five key issues below.

**1. Line 308-9. “Any recent use (e.g., within 48 hours of enrollment) of an antimicrobial therapy with a drug that has activity in the treatment of urinary tract infection”**

Precluding a single dose of antimicrobial therapy prior to enrollment in the proposed Guidance presents severe logistical challenges. Precluding the availability of even a single dose of non-study antibiotic therapy will make enrollment of patients in the U.S. all-but-impossible in the acute care setting. It is not ethical, or possible, for investigators in the U.S. to withhold antibiotic therapy from patients with cUTI during the several hours required for the enrollment process to occur. Enlisting patients takes several hours because it consists of identification of potential patients, obtaining informed consent, screening for study eligibility, drawing laboratory studies and obtaining the results for study requirements, confirming pyuria and a positive Gram’s stain of the urine, randomizing, and delivering study medication to prospective patients. It is extremely problematic to withhold therapy during that entire process. It is particularly complicated for antibiotic therapy to be withheld in Emergency Departments and Urgent Care clinics, where considerable time pressures with respect to patient flow and rapid initiation of antibiotic therapy already exist and are ever-increasing. This is a patient safety issue. We cannot ethically expose our patients to the risks of treatment delay in this setting.

The result of this requirement will be to preclude most enrollment of ill patients into these studies in the U.S. When trials that are conducted enroll >90% of their patients outside the U.S., in practice settings that are not comparable to the U.S., the trials may fail to inform practitioners or patients regarding the safety and efficacy of the drug in the U.S. setting. Indeed the data may not be generalizable to U.S. patients. Furthermore, there are complex ethical issues that are associated with driving trial enrollment in other countries. Finally, since the requirement for no prior antibiotics will preclude enrollment of more severely ill patients, and the requirement for 5 days of intravenous antibiotic therapy will preclude enrollment of less ill patients (as discussed in the next section below), we believe almost all patients with cUTI will be precluded from enrollment in acute care settings in the U.S. The guidance document needs to be flexible to include all severities of cUTI, since the severity can range from patients with only a need for a few hours in the hospital to patients who have need for many days in the hospital. **This concern is not theoretical. IDSA members who participated in the drafting of these comments have recently attempted to enroll patients in ongoing cUTI trials that are designed to these specifications, and have first-hand experience with the inability to enroll such patients.**

On the other hand, IDSA understands that FDA is concerned about the potential impact of prior antimicrobial therapy on patient outcome in the setting of a non-inferiority trial design for cUTI. For example, even in the absence of a putative curative effect, prior antimicrobial therapy could reduce urinary pathogen counts, making it more likely that study drug treatment could result in cure.

Nonetheless, in a preliminary review, we did not find recent human data to suggest that a single dose of antibiotic therapy cures cUTI, although such data do exist in the setting of the more easily treated entity of uncomplicated UTI. An exception relevant to cUTI could be that a single dose of an aminoglycoside results in therapeutic concentrations in the urine for 3 days. Therefore, we agree that one dose of an aminoglycoside in the 24 hours prior to enrollment should be an exclusion criterion. Other antibiotic classes, including cephalosporins, fluoroquinolones, etc, do not maintain concentrations in the urine for a prolonged period of time.

IDSA believes that FDA must have considerable amounts of data in its New Drug Application (NDA) database that could help inform an evidence-based decision on the need to allow a single dose of antibiotic therapy prior to enrollment in future cUTI trials. For example, an analysis of these datasets could determine whether there is a difference in urine pathogen colony counts or species distribution between patients who have received a dose of prior antibiotic therapy and those who have not. Other analyses could also be informative, including observed differences in rates of clinical cure and microbiological eradication between these groups. FDA would contribute valuable data to the field if it could conduct and publically share the results of such analyses.

One interim option for FDA to consider would be to cap enrollment of patients with prior antimicrobial therapy at, for example, 50% of all enrolled patients. So doing would allow enrollment of U.S. patients, permit sensitivity analyses of data from future clinical trials, and collect the data needed to make an appropriate, evidence-based scientific decision on this point. The Agency took a somewhat similar approach in capping the proportion of major abscess in ABSSSI trials. Nonetheless, regardless of whatever theoretical beliefs exist—in the absence of any available data that a dose of non-study antibiotics could potentially affect study outcomes for cUTI—IDSA believes that the practical and ethical concerns discussed above must be balanced, and we emphasize that new antibiotics to treat Gram negative bacteria that are resistant to all currently available oral antibiotics is an area of substantial unmet medical need.

**2. Lines 149-171. “We assume that patients with cUTI will have therapy initiated with an intravenous (IV) drug. In general, the safety and efficacy of an investigational drug should be evaluated by maintaining treatment with the investigational drug for the entire duration of treatment, if feasible, and evaluating effectiveness at that time...”**

This assumption is problematic from the perspectives both of standard clinical practice and unmet medical need. The need for new oral antibiotics to treat GNB, including cUTI, is one of the highest priority areas for antibiotics. It is common in clinical practice for patients who have cUTI, including patients with pyelonephritis who can tolerate oral medications, to receive an all-oral regimen, particularly with the excellent bioavailability and tolerability of fluoroquinolones. Such patients often do receive 1 dose of parenteral therapy (either intramuscular (IM) or IV) in Urgent Care, Emergency Departments, or other higher level of care settings. But, such therapy is not required, and outpatient treatment in an office setting may indeed be entirely oral.

Furthermore, for agents that are IV only, it is not practical, and indeed may be unethical, to require that all or even most of the treatment be administered intravenously. The large majority of patients who receive initial parenteral therapy for cUTI do not receive more than 1 or 2 days of such therapy, and are rapidly switched to oral therapy (“step down”) as soon as they can tolerate oral medications (i.e., nausea/vomiting is resolved). Exposure of patients to PICC lines poses risks that include venous thromboembolism, central line-associated bloodstream infections (CLABSI), and central venous stenosis that can lead to future chronic edema in affected extremities (and limit future hemodialysis access for patients with chronic renal failure). Even requiring a minimum of 5 days of IV therapy exposes patients unnecessarily to the risks of the central line, and makes enrollment of patients in the U.S. problematic. Thus, there are both ethical and practical problems with such a requirement.

Furthermore, since IV therapy with the newly approved agent will very rarely be given for more than a few days when the drug is used in clinical practice, it is difficult to understand how a trial requiring prolonged IV therapy establishes safety and efficacy in a manner that is consistent with how such a drug will be used post-approval. The criteria for duration of IV therapy should be curtailed—5 days is too long—and there should be no requirement for in-patient hospitalization, since IV therapy can be administered at home using a qualified home health agency. Finally, part of the problem with the 5 days of therapy is the FDA’s assumption about the standard duration of therapy for cUTI, which we discuss fully in the next section.

**3. Lines 175-176. “Although it is important for patients to receive the total duration of therapy for the treatment of cUTI (e.g., between 10 to 14 days of therapy)..”**

The belief that 10 to 14 days of therapy is standard for treating cUTI is not commensurate with modern clinical practice. It is now standard of care in most settings to treat pyelonephritis and most catheter-associated UTIs, particularly in women, for 5-7 days. Few patients require more than 7 days of therapy, and indeed as the most recent IDSA guidelines on UTI discuss, there are studies that show that 5 days of therapy are sufficient for some patients with less severe disease. The trend in infectious diseases is to treat for shorter durations of time, not longer. Even bacteremic pyelonephritis does not require more than 7 days of therapy in patients infected with typical, susceptible GNB pathogens if source control is achieved.

The recommended duration of therapy should be 7 days of therapy, with some patients being allowed to receive longer therapy if clinical circumstances demand it (e.g., UTI in the setting of obstruction which cannot be readily relieved, perinephric abscess, malignancy, lack of resolution of symptoms at day 7). The shorter duration of therapy is consistent with clinical practice, is necessary to promote proper antibiotic stewardship, and also enables shorter term evaluation of the effect of IV therapy (i.e., 3 days of IV instead of 5 required).

**4. Section A.1. Definition of Complicated UTI and B.1. Recommended inclusion criteria**

The sepsis criteria established by Roger Bone and colleagues in the 1980s are validated to indicate an increase in mortality compared to patients who do not meet sepsis criteria. We believe that any UTI in the setting of 2 of 4 standard systemic inflammatory response syndrome (SIRS) criteria (which meets the definition of sepsis) should be considered a cUTI, irrespective of other factors. Thus, we believe that, in addition to the other bulleted items listed in this section, any UTI with 2/4 SIRS criteria should be included in cUTI studies, and an additional “or” inclusion criteria should be specified in section B.1 to say “or, patients with sepsis with urinary tract signs and symptoms.”

**5. The non-inferiority (NI) margin**

A very thorough and impressive appendix is included in the document which provides justification of a non-inferiority margin for cUTI. We congratulate the FDA for doing such a thorough job and for taking on this complex task.

We note that the historical evidence of sensitivity to drug effect for antibiotic therapy for cUTI (as has been the case for other infections previously) is much greater than 20%. Indeed, the standard, highly conservative 95/95 method used by the FDA calculated a minimum treatment effect size of antibiotics of 36%—the true effect size is almost certainly greater since the 95/95 method is so conservative. Despite this large treatment effect size, the FDA has again indicated a 10% margin of NI.

The mathematical decision required to go from a 36% effect size to a 10% margin is arbitrary. There is neither a statutory nor a scientific basis for a 50% discount and then a 50% preservation of an already highly conservative estimate of antibiotic treatment effect size. The public is facing a crisis of antibiotic therapy for GNB, and cUTI is the most facile regulatory pathway to approval of new agents focused on treating GNB. Given the great unmet need for new agents to treat GNB, we strongly believe that whatever statistical comfort is gained by requiring such a narrow margin must be balanced against the requirement for a marked increase in study sample size, enrollment time, and costs that result from not allowing a 12.5% or 15% non-inferiority margin. **We emphasize that a 15% non-inferiority margin does not mean that the public is accepting a drug that is 15% less effective than the comparator drug.** The -15% margin reflects the lower bound of the confidence interval of the difference in outcome between the two arms, not the point estimate. The true difference in efficacy is far more likely to be closer to the point estimate than at the 95% CI lower bound, which is why setting a -15% margin does not mean that there is a high likelihood that a drug truly 15% worse would get approved. Indeed, as IDSA members have discussed in other settings, there is only a 1 in 400 chance that an experimental drug that is actually 15% less effective than the comparator drug would be found to be non-inferior using a -15% non-inferiority margin in two phase III trials<sup>1</sup>. This small risk is counter-balanced from a risk:benefit perspective by facilitating approval of greatly needed new antibiotics.

It is clear that antibiotics are markedly more effective for this disease than placebo. We recommend that the FDA indicate that a margin between 10% and 15% can be justified for individual protocols. Specifically, for “routine” applications for drugs similar to other agents already on the market, a margin of 10% could be acceptable if feasibility of U.S. enrollment is improved. A margin of 15% could be justified if, for example, the study drug has other critically important advantages, such as better safety, better tolerability, shorter treatment duration, or activity against multidrug-resistant UTI pathogens with limited available treatment options.

## Minor Comments

### 1. In section A.1., Definitions

It would be helpful to clarify the definition of non-pyelonephritis cUTI. What factors need to be present, aside from a Foley catheter or other catheter (e.g. nephrostomy) to make a patient eligible for cUTI studies?

Also, how will supra-pubic catheters be handled? Are they considered similar to a Foley catheter?

### 2. In section A.1., Definitions

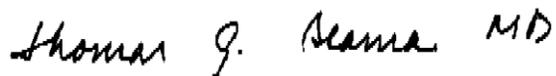
It would be helpful to clarify the definition of azotemia.

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<sup>1</sup> Spellberg B, Lewis RJ, Boucher HW, Brass EP (2011) Design of clinical trials of antibacterial agents for community-acquired bacterial pneumonia. Clin Investig (Lond) 1: 19-32.

IDSA hopes that these comments are useful to FDA as the agency moves forward to finalize the cUTI draft guidance. We would be pleased to provide clarification of any of the points raised in the letter. Should you have any questions about these comments, please contact Audrey Jackson, PhD, IDSA's senior program officer for science and research, at [ajackson@idsociety.org](mailto:ajackson@idsociety.org) or 703-299-1216.

Sincerely,

Handwritten signature of Thomas G. Slama MD in black ink.

Thomas G. Slama, MD, FIDSA  
President