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IDSA
Infectious Diseases Society of America

April 7, 2014

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Re: Comments on Docket # FDA-2009-D-0136; Draft Guidance for Industry on Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment

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Society of America (IDSA) is pleased to submit comments on the above referenced Food and Drug Administration (FDA) Draft Guidance concerning Community-Acquired Bacterial Pneumonia (CABP). IDSA represents nearly 10,000 infectious diseases physicians and scientists devoted to patient care, disease 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) enzymes 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 infections caused by multi-drug-resistant organisms (MDROs). IDSA welcomes the positive evolution of FDA's approach to regulatory guidance for MDROs as demonstrated in the CABP guidance, and we greatly appreciate the effort that FDA has put into this draft guidance. This draft signals a promising movement toward making such trials practicable in the U.S. while still providing the caliber of scientific data that will allow a reasoned judgment regarding approval. Since CABP remains a significant infectious disease problem and causes substantial morbidity and mortality in the U.S., especially among young children and the elderly, the availability of practicable, clinically relevant clinical trial guidance in this area is of great importance. We provide more detailed comments on six key issues below.

1. Prior Antibacterial Drug Therapy

IDSA understands the issues requiring the consideration of limiting the number of patients entered into CABP trials with prior antimicrobial therapy. IDSA also recognizes the current proposed limit of 25% of patients with prior therapy to be a good faith effort to make this indication one which is executable. However, we wish to point out that even at a 25% limit, there will be an issue regarding enrollment of patients in the United States. Current guidelines make therapy mandatory for the vast majority of patients in a very short time frame. This "irresistible force/immovable object" problem has resulted in major problems with U.S. enrollment in recent trials, with the result that a high proportion of patients have been enrolled from Eastern European countries. Given the differences in background disease, support facilities and other issues relative to the U.S., we have a problem with the extrapolation of the data. Moreover, clinicians will be reluctant to withhold an antibiotic from patients they believe have pneumonia, and particularly those with objective indicators of severe infection (i.e., PORT score of III or higher; CURB 65 score of 3 or higher). This will be a barrier to enrollment and potentially select for a less sick patient population.

We would ask that there be an effort to achieve an explicit balance between these competing imperatives. We would also point out that the daptomycin experience, which has appropriately raised concerns about prior therapy in CABP, was in the setting of a once-daily agent (mostly ceftriaxone for prior therapy). We also ask that consideration be given to allow greater percentages of patient trial entry if prior therapy is with a shorter half-life agent.

2. Non-Inferiority Margin

IDSA remains concerned about the FDA's selection methodology for non-inferiority (NI) margins. As evidenced by a very thorough and impressive appendix, a compelling argument has been made that there is a real effect of antimicrobial therapy on both death as well as on speed of recovery. The current proposed NI margin of 12.5% is a significant improvement over past proposals. However, IDSA further recommends that consideration be given to expanding the NI margin to 15% under special circumstances. 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 pathogens with limited available treatment options.

3. Sufficiency of Single CABP Trial

IDSA recommends FDA provide greater clarity regarding the settings in which a single trial would be adequate and potentially result in an approval. Currently, a CAPB/VABP development would likely trigger this outcome. There are other possible scenarios: What about a well-done Phase II trial with appropriate analysis (e.g., pharmacodynamics driver delineation and endpoint) in addition to the single Phase III; or, What about a single Phase III in combination with a supportive Epithelial Lining Fluid (ELF) penetration study in pneumonia patients?

4. Definition of "Important Components."

It would be helpful to clarify the definition of "important components" in the following two passages:

Ln. 362-64: *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.*

Ln. 366-68: *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.*

5. Primary Endpoint

IDSA supports the 3-5 day efficacy endpoint selection. It has been demonstrated through historical data that patients receiving antimicrobial therapy have a much higher rate of improvement in the 3-5 day time frame when compared with patients who do not receive antimicrobial therapy. However, if non-treated patients survive, the difference in improvement between the two groups decreases over time. IDSA recommends FDA provide additional clarity about the impact of late loss of effect on the adjudication of the outcome. That is, if a patient had a clear response early on, but had a subsequent relapse prior to test of cure (perhaps due to resistance emergence), how would the outcome be classified?

6. Pediatric Populations

IDSA appreciates FDA's guidance recommending that sponsors discuss drug development in the pediatric populations as early as is feasible. IDSA acknowledges that the guidance given to industry for CABP is likely to evolve over the next 5-10 years as we learn more about feasibility, the appropriate ages and circumstances for extrapolation, and the necessary sample sizes needed for safety assessments.

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IDSA hopes that these comments are useful to FDA as the agency moves forward to finalize the CABP 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 John Billington, IDSA Sr. Program Officer for Health Policy, at jbillington@idsociety.org or 703-299-0015.

Sincerely,

Barbara E. Murray M.D.

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President