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IDSA
Infectious Diseases Society of America

August 5, 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Re: Comments on Docket # FDA-2010-D-0589; Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment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Society of America (IDSA) is pleased to submit comments on the above referenced Food and Drug Administration (FDA) Draft Guidance concerning hospital-acquired bacterial pneumonia (HAPB) and ventilator-associated bacterial pneumonia (VABP). IDSA represents over 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), vancomycin-resistant enterococci (VRE), 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.

In February 2011, IDSA submitted comments on the previous draft guidance, which are available here.[1] We view this new draft as a considerable improvement and appreciate FDA's consideration of our earlier input. Specifically, we appreciate the allowance of 24 hours of prior antibacterial drug therapy before enrollment, the addition of a second primary endpoint based on survival and no diseases-related conditions, the clarification that a sponsor's choice of comparator drug should reflect the current standards of care as defined by IDSA and other authoritative scientific bodies, and the elimination of patient reported outcomes (PROs) as appropriate measurements. We offer additional detailed comments below.

[1] IDSA Comments to FDA Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP): Developing Drugs for Treatment. Letter dated February 11, 2011; *available at*: http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Position_Papers/IDSA%20Comments%20on%20HABP%20and%20VABP.pdf.

1. Prior Antibacterial Drug Therapy

We appreciate FDA's acknowledgement that "a complete ban on all patients who have received prior antibacterial therapy could. . . have adverse consequences" (*ln. 284–85*) and we applaud the agency's decision to allow enrollment of patients who have received up to 24 hours of therapy in the previous 72 hours before enrollment. As we noted in our February 2011 comments on the previous draft guidance, the great majority of patients who are hospitalized long enough to develop HABP/VABP will have been exposed to some antibiotic(s) during their hospitalization, and therefore requiring no antibiotics within 30 days will eliminate from eligibility most HABP/VABP patients. Moreover, obtaining informed consent from HABP/VABP patients who are sedated and suffering physiological derangement will be very difficult.

Even with the 24 hour allowance, however, we are concerned that enrollment will still be difficult under certain circumstances, and therefore we recommend that FDA consider allowing more than 24 hours under certain circumstances. For example, if the diagnosis of the pneumonic process is by broncho-alveolar lavage (BAL), and in the specimen from the BAL, the patient has >10^4 cfu/ml of bacteria, then prior antibiotic therapy of any duration should be acceptable (*i.e.*, the patient would still qualify by definition in spite of prior therapy). In addition, given the critical need for alternatives and development of agents with unique activity, other strategies to enhance enrollment should be considered, including anticipatory informed consent procedures as illustrated in the draft guidance.

2. Noninferiority Margins

IDSA is 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 10%, while consistent with IDSA recommendations in 2010-2011, fails to take into account the immediate crisis faced by HABP/VABP patients with no therapeutic options. As such, IDSA 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. Primary Endpoint

IDSA supports the primary endpoint selected (all-cause mortality between 14-28 days) and appreciates the addition of a second primary endpoint. Limiting trials to a mortality-only primary efficacy end point is not consistent with standard clinical practice. We reiterate here that new studies should be conducted by industry and academia to reevaluate existing datasets to establish antibacterial effect size for clinically meaningful endpoints. In the meantime, however, IDSA supports FDA's willingness to discuss disease related complications with sponsors in advance of trial initiation.

4. 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 HABP/VABP 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.

5. Definition of "Important Components."

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

> Ln. 374-75: *Per-protocol populations — Patients who follow important components of the trial as specified in the protocol.*
>
> Ln. 377-79: *Per-protocol microbiologically evaluable populations — Patients who follow important components of the trial as specified in the protocol and have a baseline bacterial pathogen identified as the cause of HABP/VABP.*

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IDSA hopes that these comments are useful to FDA as the agency moves forward to finalize the HABP/VABP draft guidance. Should you have any questions about these comments, please contact John Billington, IDSA Senior Program Officer for Health Policy, at jbillington@idsociety.org or 703-299-0015.

Sincerely,

Barbara E. Murray M.D.

Barbara E. Murray, MD, FIDSA
President