IDSA Headquarters
1300 Wilson Boulevard
Suite 300
Arlington, VA 22209
TEL: (703) 299-0200
FAX: (703) 299-0204
E-MAIL ADDRESS:
info@idsociety.org
WEBSITE:
www.idsociety.org

IDSA
Infectious Diseases Society of America

October 17, 2011

Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave., Bldg. 1, Rm. 2217
Silver Spring, MD 20993

Dear Commissioner Hamburg:

I write on behalf of the Infectious Diseases Society of America (IDSA) to further our ongoing discussion regarding regulatory challenges in the antibacterial and influenza antiviral drug development and approval pathways. You are well aware of the imminent public health crisis with the potential to affect our nation's security resulting from the simultaneous increase in antimicrobial drug resistance and the decrease in the development and rate of approval of new drugs. IDSA appreciates the Food and Drug Administration's (FDA) recent efforts in producing new antibacterial drug clinical trial guidelines. However, we are concerned that these guidelines still do not create feasible pathways for conducting antibacterial drug trials. In addition, pharmaceutical companies are continuing to eliminate or downsize their antibacterial research and development (R&D) portfolios. The current situation is untenable, and the remaining antibacterial R&D programs hang in a fragile balance. Similar challenges arise from FDA's current approach to clinical trials design for influenza antivirals, particularly parenteral antivirals for hospitalized patients who are too sick to be treated with placebo.

We understand the difficulties that FDA faces in weighing the risks versus benefits in this area where the regulatory science is deficient. IDSA is supportive of FDA and sensitive to the agency's constraints, but we remain deeply concerned. We jointly seek the same outcome: new, safe and effective anti-infective drugs. Unfortunately, at this time, the micro-organisms are evolving faster than we are.

For this reason, IDSA asks that you engage with the Institute of Medicine (IOM) to discuss options for developing a process to review the operational feasibility of FDA's current approaches to the design of antibacterial drug and influenza antiviral drug clinical trials.

The IOM could:

- **assess the limitations and strengths of FDA's current statistical approaches;**
- **provide new perspectives on approaches to balancing public health risk vs. benefit of decisions that must be made, even in the face of incomplete or imperfect data, and applied to the evaluation of the safety and efficacy of new anti-infective drugs; and**
- **make recommendations leading to more rapid improvements in regulatory science.**

Reaching out to IOM for its expertise at this time would be consistent with the ideals set out in FDA's recently released blueprint for "Driving Biomedical Innovation: Initiatives to Improve Products for Patients". In that report, FDA noted:

"During the HIV epidemic in the early 1990s, experts from many fields came together to rapidly work through the science underlying the disease and devise programs for AIDS drug development. The result was a relatively efficient development process and availability of effective anti-HIV drugs."

We need exactly that kind of initiative now in other areas of anti-infective drug development. IDSA leaders appreciate that, despite less than optimal human and financial resources, FDA is aggressively modernizing and clarifying anti-infective guidance documents. However, as IDSA leaders have noted in meetings with you and other FDA officials and in our formal comments, significant feasibility concerns persist with proposed guidances for Community-Acquired Bacterial Pneumonia (CABP), Hospital-Acquired Bacterial Pneumonia (HABP)/Ventilator-Associated Bacterial Pneumonia (VABP) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI). IDSA also remains concerned about the need for feasible guidances in areas relevant to resistant Gram-negative bacterial infections, such as non-inferiority trials of complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), organism-specific trials, and superiority trials. IDSA recently provided a similar assessment of FDA's guidance for developing influenza antivirals for treatment and/or prophylaxis in our comments submitted to the public docket on October 12. FDA's guidances, in some instances, appear to deviate substantively from standard clinical care and thereby may impede, rather than facilitate, anti-infective drug development. The realities of patient care may not allow compliance with regulatory guidance.

Our greatest concern is the statistical approaches the agency is employing. It seems that many of the troublesome areas in the draft guidances result from, or are strongly influenced by, the desire for unqualified clinical data, like mortality, that is easily analyzed statistically. FDA's current approaches particularly impact study designs where the infection/disease is acute, life-threatening, and for which a placebo group has not been and cannot now be included. The clinical reality in these patients is that successful treatment is measured by reduction of fever, return of appetite, and normalization of biomarkers. We believe that statistical analysis should include such clinically relevant endpoints as well as microbiologic endpoints addressing the elimination of the infectious pathogen.

In our earlier comments on the FDA draft HABP/VABP guidance, IDSA communicated two key points designed to improve the feasibility of HABP/VABP clinical trials: i.e., allowance for a brief period of antibiotic therapy prior to clinical enrollment; and the use of biomarkers as an adjunct and/or alternative to the collection of traditional respiratory culture specimens. Clinically, it is not possible to withhold the first dose of empiric therapy in HABP/VABP patients. These infections are caused by virulent highly antibiotic-resistant bacteria, occur in very debilitated hosts, and are treated with short half-life drugs, often in the setting of a foreign body (endotracheal tube). There is little chance that a single dose of a short-acting antibiotic is going to alter the clinical course of such infections. With regard to the proposed guidance for ABSSSI, the refusal to allow a single dose of a non-study antibiotic will make enrollment very

challenging. These same issues complicate trial designs for other areas mentioned above, including CABP, UTI, cIAI, etc. It is our understanding that many industry representatives also perceive FDA's proposed ABSSSI, CABP, and HAPB/VABP guidances to be infeasible to follow. In IDSA's recent comments on FDA's influenza antivirals guidance, we communicated that the guidance does not provide a realistic trial design for hospitalized patients, as the currently proposed designs would require unrealistically large numbers of patients and likely generate an outcome of non-superiority compared to available single agent neuraminidase inhibitor therapy. Instead we argued that an active-controlled, non-inferiority trial would not only be valid in hospitalized patients, but also would serve to promote more rapid antiviral drug development in the United States. Moreover, aspects of FDA's anti-infective guidances raise ethical concerns.

The leading reason that companies voice for the dramatic decrease in new anti-infective R&D is the lack of clear and feasible instructions from FDA. Despite numerous joint workshops held by FDA and IDSA and the work of multiple FDA advisory committees, the perception of impossible regulatory hurdles persists. During a recent meeting hosted by IDSA, the Pew Health Group and the Pharmaceutical Research and Manufacturers Association (PhRMA), representatives from the few companies that remain in antibacterial drug development reported that FDA's current course is leading them to focus their future efforts on European, Asian, and Latin America markets and not on the United States. As physicians who treat patients in the U.S., we believe it is extremely important that antibacterial trials be designed in a fashion that permits them to be conducted in this country to ensure their results are generalizable to U.S. patients. We believe that the IOM could help break the logjam with an unbiased review, rooted in scientific expertise, and accelerate your goal of improving regulatory science. IOM recommendations could help advance a process in desperate need of momentum to the benefit of U.S. public health and national security.

We hope you will seriously consider our request. We look forward to continuing to work with you and FDA staff to achieve a realistic and viable regulatory pathway that will re-invigorate antibacterial and influenza antiviral drug discovery and development. Please contact Robert J. Guidos, JD, IDSA's vice president for public policy and government relations, should you have any questions or comments, at rguidos@idsociety.org or 703-299-0200.

Sincerely,

James M. Hughes, MD, FIDSA
President