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

IDSA
Infectious Diseases Society of America

September 30, 2013

[By Electronic Submission to www.regulations.gov]

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

Re: Comments on Docket No. FDA-2013-D-0744; Draft Guidance for Industry on Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Diseases

Dear Sir/Madam:

IDSA is pleased to offer comments on the draft document "Guidance for Industry: Antibacterial Therapies for Patients with Unmet Medical Need for the Treatment of Serious Bacterial Infections." IDSA represents over 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), vancomycin-resistant enterococci (VRE), multidrug-resistant *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and emerging infections such as that caused by the 2009 H1N1 influenza virus.

IDSA has long highlighted the serious threats of antibiotic resistance and the anemic antibiotic pipeline. Most recently, an IDSA report issued in April[1] identified only seven new drugs in development for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (GNB). IDSA remains committed to advancing policies to stimulate the development of new antibiotics that patients desperately need. In order to meet this goal, we need feasible clinical trial designs for new antibiotics.

On September 16, 2013, the Centers for Disease Control and Prevention (CDC) released a comprehensive report on "Antibiotic Resistance Threats in the US, 2013. The report highlights how this growing threat and the loss of effective antibiotics

[1] Boucher HW, et al. 10 × '20 progress—Development of new drugs active against Gram-negative bacilli: An update from the Infectious Diseases Society of America. Clin Infect Dis. 2013; 56(12):1685-94.

undermine our ability to fight infectious diseases. CDC conservatively estimates that approximately 2 million people are infected with resistant bacteria with over 20,000 deaths per year. Those numbers are likely far higher, as our current surveillance and data collection capabilities cannot capture the full burden. The societal costs are huge in not only attributable deaths, but also excess healthcare costs estimated to be over 20 billion dollars. Complicating this challenge is the unmet need for new treatments for serious and life-threatening infections. The CDC recommended four core actions: 1) preventing infections and preventing the spread of resistance, 2) tracking resistant bacteria, 3) improving the use of today's antibiotics, and 4) promoting the development of new antibiotics and diagnostic tests for resistant bacteria.

The President's Council of Advisors on Science and Technology (PCAST) recommended in their 2012 report that the FDA create a new "special medical use" (SMU) designation for the approval of drugs for subpopulations of patients with unmet needs. Certainly antibiotics for multi-drug resistant organisms fit this definition. IDSA has endorsed the establishment of the Limited Population Antibacterial Drug (LPAD) approval pathway for new antibiotics to treat serious or life-threatening infections for which few if any treatments currently exist. This new pathway would allow FDA to quickly approve novel antibiotics on the basis of trials conducted on smaller subpopulations with the most serious illnesses since it is often not feasible to test new antibiotics for these infections using traditional large trials. Drugs approved under this new pathway should have a special designation, logo and label. LPAD legislation would provide additional critical safeguards to help ensure appropriate, narrow use of these new drugs. While awaiting legislative activity, IDSA supports FDA's efforts to encourage antibacterial drug development geared toward unmet medical needs. Specifically, IDSA has emphasized the importance of timely publication of a document to provide guidance on streamlined testing along with clinical trial designs for FDA approval.

We applaud the FDA for proposing this draft guidance. The document is thoughtful and covers many important questions. Drugs approved under this mechanism should have clear labeling information that includes the limited population for whom these drugs are indicated. The labeling information should also make clear that these drugs carry a less precise estimate of benefit : risk ratio than drugs approved under traditional large-scale clinical trials. Such information is critical to guide appropriate use of these drugs, which protects patients and limits the rate at which resistance to these drugs develops.

We strongly agree that pre-specified endpoints and the design of trials should be agreed upon before trials are conducted. The choice of the margins should also be discussed in advance of trial initiation as the document supports. On page 7, we offer a comment on the following statement: "Sponsors considering a trial design that relies on a historical control based on a retrospective review should characterize the proportion of patients with the clinical outcome of interest when given no therapy or inadequate therapy." This could also apply when the currently available treatment is inadequate. We agree that companies should still be required to demonstrate that the drug is safe and effective under the conditions prescribed, recommended, or suggested in its labeling. Lastly, we agree that encouraging development of several drugs for the same or similar indications is important to address adverse effects, development of resistance or drug shortages.

Since approval for drugs under this guidance may involve smaller, shorter, or fewer trials, it is imperative that a mechanism be developed to do post-marketing monitoring. One suggestion is to require a registry to monitor for side effects, outcomes, and appropriate use. The CDC's National Healthcare Safety Network (NHSN) and other existing programs should be considered as a monitoring tool for these drugs. The monitoring mechanism and funding for such a registry should be in place prior to approval. In addition, FDA should consider coordinating with the Centers for Medicare and Medicaid Services (CMS) and the CDC to ensure efforts are in place to promote the appropriate use of all antimicrobial drugs, especially those approved through these more streamlined programs.

Lastly, IDSA also strongly encourages the development and use of rapid diagnostic tests in identifying patients with multidrug resistant pathogens. Once a drug is approved, diagnostic tools will be critically important to help guide appropriate use of the new drugs.

IDSA hopes that these comments are useful to FDA as the agency moves forward to develop new approaches for the development of antibacterial drugs for patients with unmet medical needs. The Society remains committed to patients who desperately need new antibiotics. Feasible clinical trial designs are necessary to meet this growing need and save patients' lives. Should you have any questions, please contact Amanda Jezek, IDSA's Vice President of Public Policy and Government Relations at ajezek@idsociety.org or 703-740-4790.

Sincerely,

David A. Relman, MD, FIDSA
President