Food and Drug Administration (FDA) Public Meeting
Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD Pathway)
Statement by the Infectious Diseases Society of America
July 12, 2019

The Infectious Diseases Society of America thanks the Food and Drug Administration for holding today's meeting to discuss the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD). IDSA represents over 11,000 infectious diseases physicians, scientists, public health practitioners and other health care providers. Our members care for patients with serious, life-threatening infectious diseases, including those caused by multidrug-resistant pathogens with few or no treatment options. Our members also conduct research on antimicrobial resistance and the development of new therapeutics and lead antimicrobial stewardship programs. IDSA first sounded the alarm about the crisis of antimicrobial resistance and the need to invest in new antibiotic research and development in 2004. Since then, IDSA has led efforts to advance policies to stimulate new antibiotic R&D and promote appropriate antibiotic use, including legislation to enact LPAD. Today, IDSA underscores the importance of this pathway, as the state of the antibiotic pipeline has grown even more dire. We are also pleased to offer some recommendations to strengthen the draft LPAD guidance to expand opportunities for antibiotic R&D.

IDSA greatly appreciates the FDA recognizing the gravity of antimicrobial resistance and the fragility of the antibiotic pipeline. Very few large companies remain engaged in antibiotic discovery and development, and the small companies who are driving the vast majority of antibiotic innovation are struggling to stay in business. Without a robust and renewable antibiotic pipeline, increasing numbers of once treatable infections will become deadly, and modern medical advances like chemotherapy, transplants and other complex surgeries could become too dangerous to perform, undoing decades of progress against disease. The opioid epidemic is adding further urgency to the crisis of AMR, as injection drug use is causing increasing numbers of infections caused by resistant pathogens. The CDC reported that people who inject drugs are 16 times more likely to develop an invasive MRSA infection.

The limited population pathway is essential to strengthening our antibiotic pipeline because many of the deadliest infections with the fewest treatment options currently occur in relatively smaller numbers of people who are often critically ill, which makes traditional, large-scale clinical trials infeasible. Further, new antibiotics with activity against the most difficult-to-treat pathogens should be used only in the patients who truly need them to protect their utility against the development of resistance. The limited population pathway addresses both of these challenges and, if properly utilized, can help bring to market some of the most urgently needed new antibiotics and promote their appropriate use.

IDSA supports the policies and processes outlined in the draft guidance. We are pleased to offer some recommendations that we believe will strengthen the ability of the limited population pathway to bring new antibiotics to market with urgently needed indications. To maximize the potential of this new pathway, the use of novel trial designs will be critically important. Further, while non-inferiority trials are often most appropriate for studies of new antibiotics, some of the small studies conducted under this new pathway may not be amenable to non-inferiority design.

In instances for which superiority designs would be appropriate under the new pathway, the FDA should consider using $p < 0.1$ or another less stringent value for type 1 error control if the risk-benefit ratio is favorable. In some instances, it may be appropriate to include data from patients in other countries, given that certain multidrug-resistant pathogens may be more prevalent in countries other than the US.

It is important to remember that in addition to new antibiotic approvals, the new pathway also offers important opportunities to promote and monitor appropriate antibiotic use via the statutory requirements that drugs approved under this pathway be clearly labeled as "Limited Population" and that their use is monitored. By approving a new antibiotic for a traditional indication and not a limited population indication, the FDA may essentially forfeit these valuable stewardship opportunities.

IDSA understands that approval for limited population indications may not always be feasible or appropriate for sponsors seeking this route. In such instances, the FDA should utilize other tools at its disposal to incent antibiotic R&D and to provide critically needed new treatment options. Flexibility in the package insert language for drugs and studies meeting the LPAD criteria but not necessarily meeting FDA indications for approval in that disease syndrome may provide a meaningful incentive to drug sponsors and useful information for clinicians. Package insert language is essential because it informs clinical decision-making and governs sponsor communications regarding its products. Even if a sponsor cannot achieve a limited population indication for a new antibiotic, IDSA recommends the sponsor still be able to share its study data from use of the new drug in patients with resistant infections. Given our extremely limited antibiotic arsenal and increasing rates of antibiotic-resistant infections, clinicians are frequently forced to rely upon treatment options based on extremely limited clinical or even *in vitro* data. In this environment, additional data that could inform how a new antibiotic may perform in a patient with a difficult-to-treat infection would be very useful.

Finally, IDSA would like to emphasize that LPAD plays a vital role in the broader national and global fight against antimicrobial resistance, but much more work is needed to foster the antibiotic pipeline necessary to meet current and future threats and to stem the tide of antimicrobial resistance. The FDA has an important role as a champion within our government for broader solutions. IDSA calls for antibiotic reimbursement reform and novel pull incentives, such as a market entry reward for targeted, urgently needed new antibiotics that address our greatest unmet needs to ensure fair and reasonable returns on investment for antibiotic R&D. We also support higher investments in AMR research and clinical trials networks. Equally important, IDSA continues to advocate for a federal requirement for all health care facilities to adopt antibiotic stewardship programs that align with CDC recommendations. We also support increased funding for our public health system to address AMR. Lastly, we urge a federal commitment to sustain the expert workforce needed to effectively combat AMR on all fronts—patient care, research, stewardship, infection prevention and control, and public health.

Once again, IDSA thanks FDA for its continued efforts to strengthen the antibiotic pipeline and promote the appropriate use of these precious drugs.