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IDSA
Infectious Diseases Society of America

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Leslie Kux
Associate Commissioner for Policy
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Docket No. FDA-2018-D-2032 for "Limited Population Pathway for Antibacterial and Antifungal Drugs; Draft Guidance for Industry; Availability."

Dear Associate Commissioner Kux:

The Infectious Diseases Society of America greatly appreciates the opportunity to comment on the draft guidance, "Limited Population Pathway for Antibacterial and Antifungal Drugs." IDSA represents over 11,000 infectious diseases physicians and scientists. 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. 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 legislation to stimulate new antibiotic R&D, including legislation to enact the limited population pathway. IDSA underscores the importance of this pathway, appreciates the draft guidance, and offers some recommendations to strengthen the guidance to expand opportunities for antibiotic R&D.

Urgent Need for New Antibiotics and the Limited Population Pathway

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, while patient needs for new antibiotics continue to grow. 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 limited population pathway is essential to strengthening our antibiotic pipeline because many of the deadliest infections with the fewest treatment options occur at the moment in relatively smaller numbers of people 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 utilized, can help bring to market some of the most urgently needed new antibiotics and promote their appropriate use.

Flexible Trial Designs

IDSA supports the policies and processes outlined in the draft document. 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, 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 other countries than in the US.

Labeling and Monitoring

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 important stewardship opportunities. Further, it is likely that many antibiotics in such instances would be used off-label anyway given the lack of safe and effective therapeutic alternatives and growing patient need.

Package Insert Language

IDSA understands that approval for limited population indications may not always be feasible or appropriate for sponsors seeking this route. In such instances, 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 important 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.

Broader Stewardship Efforts

Finally, IDSA would like to emphasize the important role of this draft guidance and the limited population pathway in the broader national fight against antimicrobial resistance. As we continue to advance the implementation of ID physician-led antibiotic stewardship programs in healthcare facilities across the country, we hope that the strength of these efforts will provide further

confidence that new antibiotics approved under the limited population pathway will be used appropriately and, thus, provide FDA the confidence to utilize the new pathway. The Centers for Disease Control and Prevention has reported that in 2016, 69.5 percent of general acute care hospitals had implemented stewardship programs aligned with the CDC core elements for stewardship. This is an increase from 53.1 percent in 2015 and 44 percent in 2014. While this progress is encouraging, IDSA is continuing to advocate for a Medicare Condition of Participation that would require all hospitals to implement stewardship programs.

Once again, IDSA thanks you for your continued efforts to strengthen the antibiotic pipeline and promote appropriate use of these precious drugs. If we can be of any assistance to you in these efforts, please do not hesitate to contact Amanda Jezek, IDSA's Senior Vice President for Public Policy and Government Relations at ajezek@idsociety.org or 703-740-4790.

Sincerely,

Paul G. Auwaerter, MD, MBA, FIDSA
President, IDSA