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November 17, 2016

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

Re: Docket No. FDA-2016-D-2561; Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test (AST) Devices

Dear Sir/Madam:

The Infectious Diseases Society of America (IDSAs) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) draft guidance, "Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test (AST) Devices." IDSAs shares the FDA's stance that AST devices enable clinicians to make guided therapeutic decisions that are critical to safe, effective patient care while aiding in the fight against antimicrobial resistance. More must be done to ensure the timely availability of AST devices for patients, physicians and clinical laboratories. We applaud the federal government pursuing efforts to advance the National Action Plan for Combating Antibiotic Resistant Bacteria (CARB). Critical elements incorporated include implementing antimicrobial stewardship programs at all hospitals and long term care facilities and incentivizing the development of new antibiotics and diagnostic tests. This guidance presents an important opportunity to advance AST devices that are necessary for directing the optimal use of antimicrobial drugs.

Under current policy, AST device manufacturers may not submit their 510(k) for susceptibility testing of a new antimicrobial agent until that agent has been approved by FDA. This, combined with other barriers to AST device development, typically results in a 3-5 year gap between the introduction of a new antimicrobial agent on the market and the availability of an FDA-cleared AST device that can test the new agent. This gap not only impairs laboratories' ability to inform clinical decision making, it discourages the development of new antibiotics and AST devices, both of which are urgently needed.

The draft guidance recognizes the vital interplay that pharmaceutical companies and AST device manufacturers coordinate their efforts long before a new antimicrobial agent is approved. IDSAs strongly supports this initiative and is pleased to offer additional recommendations to further strengthen this guidance. In addition, IDSAs looks forward to working with the FDA, Congress, and other stakeholders to advance broader policies to incentivize the timely development of AST devices.

Background: How lack of AST Devices Harms Patient Care

When susceptibility testing data are not available, physicians struggle to use newly approved antibiotics wisely. Physicians are currently facing increasing numbers of patients with serious infections caused by multidrug resistant organisms (MDROs). Many older antimicrobial agents are ineffective when used alone and may also pose toxicity risks. New antimicrobials can be efficacious and less toxic, providing needed options for physicians and vulnerable patients. However, without susceptibility test

results, the physician must choose treatment without really knowing the likelihood of treatment success. This fosters reluctance to use the new agents. The unfortunate result is that physicians and their patients are essentially left without access to these new important life-saving antimicrobial agents, thus further limiting the already dangerously small arsenal of drugs to treat MDRO infections. This has the very real effect of potentially costing lives – as drugs that might be effective are not being used. In addition, this hesitancy to appropriately use new antimicrobial agents erodes an already often meager return on investment for new antibiotics. This discourages antibiotic research and development (R&D) at a time when we must do all we can to strengthen the very modest antibiotic pipeline.

Moreover, antimicrobial stewardship programs, which will soon be required in all hospitals and long term care facilities, are also challenged without the specific susceptibility data provided by AST devices.

Additional Recommendations

IDSA supports the draft guidance's efforts to speed the inclusion of new antimicrobial agents on AST devices. We recommend that the guidance take the additional step of explicitly permitting and encouraging AST device developers to submit 510(k) applications before a new antimicrobial agent is approved. We also recognize that developers may be hesitant to undergo the significant burdens of AST device development for new agents that may ultimately not be approved. Therefore, the federal government should actively work to reduce such burdens in order to encourage AST device development to begin the process as swiftly as possible. These efforts should also include ongoing coordination between FDA's Center for Drug Evaluation and Research and Center for Devices and Radiologic Health.

Improving Access to Specimens and Isolates

Significant challenges for AST device developers include gaining access to appropriate specimens such as isolates from the drug's clinical trials and validated, new panels. Current policy requires developers to collect and provide data on a minimum of 100 fresh isolates (no more than 7 days old) from at least three clinical sites. IDSA recognizes that developers must produce sufficiently robust data to ensure that new AST devices provide reliable results. However, we believe this can be done in a much more flexible manner that reduces development time and cost. IDSA recommends that the draft guidance permit and encourage the use of older, frozen specimens such as isolates that have been collected during antimicrobial drug clinical trials and those available from high quality repositories such as the [FDA-Centers for Disease Control and Prevention \(CDC\) Antimicrobial Resistance Isolate Bank](#), the [Antibacterial Resistance Leadership Group \(ARLG\) Virtual Biorepository Catalogue](#), or the [Department of Defense's Multidrug-resistant Organism Repository and Surveillance Network \(MRSN\)](#).

Provide Fast Track and Priority Review Status to AST Devices

IDSA strongly encourages FDA to provide Fast Track and Priority Review for AST test devices. There is broad stakeholder agreement that it is in the best interest of patients and public health for AST testing. This includes both new antimicrobial agents and those agents with revised breakpoints. Such devices should be brought to market as quickly as possible, as they are an essential tool for guiding the optimal use of antimicrobial agents.

Allow AST Devices to Cover More Organisms Beyond Drug Indication

Under current policy, AST devices are developed to test for the susceptibility of organisms included in the antimicrobial drug's indication or label. However, during clinical trials performed for FDA approval, there may be an inadequate number of infections by specific pathogens to determine if the drug could be sufficiently efficacious to meet the FDA requirement for a clinical indication. Therefore, those potential pathogens are not included in the drug treatment indications and there are no AST interpretations provided for use by the clinical microbiology laboratory. The establishment of clinically relevant, accurate, and reproducible susceptibility data for pathogens not covered by the

antimicrobial agent's intended use could provide valuable additional data for clinicians to consider in the context of MDRO's with very few treatment options. Widely available susceptibility data could also be central for detection of new resistance trends for these agents within important bacterial families.

Improve Access to New Antimicrobial Agents for AST Device Development

AST device developers need access to a new antimicrobial powders in order to develop and test new AST devices. Currently, there are barriers in obtaining new agents that impede test development. IDSA is hopeful that the early interactions between pharmaceutical companies and device developers encouraged by this guidance will help address this challenge. We recommend that the draft guidance go a step further. We suggest pharmaceutical companies make new antimicrobial agents readily available to AST device manufacturers as early in the development process as possible. While IDSA supports speeding FDA approved AST devices to market, we do recognize that lag times between approval of a new antimicrobial agents and availability of a corresponding AST device will continue until new policies are implemented.

To help bridge this gap, IDSA recommends that the draft guidance encourage pharmaceutical companies to make new antimicrobial compounds available to select clinical laboratories and research reference laboratories with expertise and capability to perform reference broth or agar dilution MIC tests according to CLSI reference methods. This alternative will allow high complexity clinical laboratories to provide susceptibility testing data to physicians until an FDA approved AST device is available. We recognize that many clinical laboratories do not have the expertise or capacity to develop, validate, and provide susceptibility testing using broth or agar dilution methods. Thus, this recommendation is limited to those laboratories with demonstrated expertise. IDSA urges FDA to strike an appropriate balance on this issue. IDSA would be pleased to provide experts to work with the FDA to develop criteria for clinical laboratories that are capable of proving results on newly approved antimicrobial agents to physicians via standard CLSI AST reference methods.

A Look Ahead

IDSA lauds the draft guidance. We hope the FDA will adopt our recommendations to further strengthen its impact. We also recognize that additional work will be necessary to comprehensively stimulate the inclusion of new antimicrobial agents on AST devices. As the agency works with other stakeholders and Congress on this issue, we urge you to consider the following opportunities for progress.

Updating Antimicrobial Susceptibility Breakpoints

The inclusion of new antimicrobial agents on existing AST devices is essential. It is equally critical that the breakpoints for existing agents be updated in a timely manner to allow AST devices to keep pace with the development of resistant bacterial strains so they can continue providing accurate susceptibility data to clinicians. While FDA has made progress in updating breakpoints, the current process is too time-consuming and arduous. IDSA strongly supports Section 2121 of the 21st Century Cures Act, H.R. 6 that would streamline the process of updating breakpoints. Specifically, the legislation permits FDA flexibility in utilizing external standard-setting organizations, if deemed appropriate, to update drug labels and AST devices, and establishes a new website for the most updated breakpoint information. We are pleased that this legislation has already passed the House of Representatives with strong bipartisan support and continue to urge the Senate to act on this issue promptly.

Clinical Trials Networks

Greater efficiencies in clinical trials could help reduce the time and costs associated with AST device development. The recommendations discussed above, namely improving access to specimens and providing Fast Track and Priority Review, can be important steps forward. However, innovative clinical trials networks for AST devices, other rapid microbiologic diagnostic tests, and antimicrobial

agents also hold significant promise. We encourage the FDA to work with other stakeholders to further explore options for developing such clinical trial networks, including building upon the existing ARLG, modeling upon the successful AIDS Clinical Trials Group (ACTG), and collaborating with multinational efforts being led by the Wellcome Trust.

Economic Incentives

Lastly, IDSA remains concerned that the development of AST devices is costly, and that insufficient financial incentives exist for developers to bring these tests to market quickly. This is particularly true for the development of tests for antimicrobial agents that have not yet been approved, making the investment for a device manufacturer a much greater risk. However, this early development of tests is essential to close the gap between the availability of a new antimicrobial agent and the ability to provide susceptibility data for that agent. We strongly encourage the FDA to work with other stakeholders and Congress to explore opportunities to provide economic incentives for AST device development, including appropriate reimbursement, tax credits, and other financial rewards, to mitigate investment risk. As the federal government advances important efforts to incentivize antibiotic research and development, it should consider ways to also incentivize the co-development of AST devices.

Once again, IDSA thanks FDA for the development of this draft guidance and its recognition of the need to promote the timely development of AST devices. These tests are vital for providing high quality patient care and an essential component to broader efforts fighting antimicrobial resistance. We look forward to continuing to work with the FDA and other stakeholders on this important issue.

Sincerely,

A handwritten signature in cursive script that reads "Bill Powderly". The signature is written in black ink and is positioned above the typed name.

William G. Powderly, MD, FIDSA
President, IDSA