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October 19, 2017

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

ATTN: Docket No. FDA-2017-N-3854

Re: Public Workshop Comments – Antimicrobial Susceptibility and Resistance: Addressing Challenges of Diagnostic Devices

Dear Sir/Madam:

The Infectious Diseases Society of America (IDSA) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) September 13, 2017 public workshop on "Antimicrobial Susceptibility and Resistance: Addressing Challenges of Diagnostic Devices" as part of an ongoing dialogue generated by the 2016 FDA draft guidance, "Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test (AST) Devices."

IDSA shares the FDA position that approved AST devices enable clinicians to make guided therapeutic decisions that are critical to safe, effective patient care while helping to avoid unnecessary, empiric use of antibiotics—assisting them in the fight against antimicrobial resistance. We applaud the agency for engaging the diagnostics community in the scientific and the regulatory challenges associated with developing AST devices. We agree that more must be done to ensure availability of laboratory-based AST devices for patients and clinicians. Also, IDSA 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

Physicians now face increasing numbers of patients with serious infections caused by multidrug resistant organisms (MDROs). When susceptibility testing data are unavailable, physicians struggle to use newly approved antibiotics that may target these difficult MDROs. Many established antimicrobial agents are increasingly ineffective against MDROs when used alone and may 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 all of the necessary data required to predict the likelihood of treatment success for their patient.

This fosters hesitation to use new agents. Though approved for use, this means that physicians and their patients are essentially left without access to these new and life-saving antimicrobial agents, and instead rely upon an already dangerously small arsenal of drugs available to treat MDRO infections. This has the very real

effect of costing lives, as drugs that might be effective are not being used. In addition, this disinclination to appropriately use new antimicrobial agents erodes the return on investment for new antibiotics that is already often meager for companies taking the risk to produce such drugs. 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, required in all hospitals and long term care facilities, are also challenged to assist in therapy without the specific susceptibility data provided by AST devices.

Additional Recommendations

AST regulation presents an important opportunity to provide devices that are necessary for directing the optimal use of antimicrobial drugs. IDSA supports FDA efforts to speed the inclusion of new antimicrobial agents on AST devices. We recommend that AST device developers be explicitly allowed and encouraged 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 developers to begin the process as swiftly as possible. These efforts should also include ongoing coordination between FDA Center for Drug Evaluation and Research and Center for Devices and Radiologic Health.

Increase Coordinated Development of ASTs and Decrease Time to Market

Under current policy, AST device manufacturers may not submit their 510(k) for susceptibility testing of a new antimicrobial agent until that drughas been approved by FDA. This, combined with other barriers to AST device development, typically results in a 3-5 year gap between the market introduction of a new antimicrobial agent and the availability of an FDA-cleared AST device. This gap means laboratories are unable to inform clinical decision-making. This barrier also discourages the development of new antibiotics and AST devices. At the September FDA workshop, it was suggested that drug sponsors provide device manufacturers with the list of indicated organisms at the time of the NDA filing; this would allow manufacturers to prepare better and collect the appropriate organisms, including those that the sponsor indicates could be problematic.

Improve Access to Specimens and Isolates

Significant challenges for AST device developers include gaining access to appropriate specimens that could include isolates from the drug's clinical trials. Current policy requires developers to collect and provide data on a minimum of 100 fresh isolates (each no more than 7 days old) from at least three clinical sites. At the September 2017 workshop, there was strong consensus that the current 7-day rule is neither practical nor necessary, and that the definition of fresh isolates should be expanded to one month or more. Additionally, while most participants agreed with the FDA perspective that fresh samples are necessary to assess real-world validity, attendees felt that the existing requirement of 300 clinical isolates lacks a scientific basis. Rather, a mathematical model should be established to inform new general standards for device accuracy and determine performance requirements. Depending on the drug, the organism, resistance determinants and the associated breakpoints, the number and the ratio of isolates should be flexible.

To further improve access to specimens and isolates, IDSA also recommends that FDA permit the use of older, frozen, well-characterized isolates that have been collected during antimicrobial drug clinical trials. Another source should include 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). FDA should also consider the application of the Agency's Replacement Reagent and Instrument Family Policy to AST devices. This policy is used for validating and documenting changes to cleared test systems that do not significantly affect the safety and effectiveness of the device. Alternatively, FDA may consider developing a specific AST policy that is similar in spirit. Such changes would facilitate the addition of new antibiotics and instrument extensions to well-established existing families of instruments. Quicker adoption of new breakpoints and the modifications necessary to the instrumentation and the software are necessary to keep AST systems current.

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 rapid availability of AST testing is in the best interest of patients and public health. AST test devices for new antimicrobial agents must also include revised breakpoints. Such devices should be brought to market as quickly as possible as essential tools for optimal use of antimicrobial agents.

Allow AST Devices to Cover 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 drug 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 for those pathogens to meet the FDA requirement for a clinical indication. Therefore, those potential pathogens are not included in the drug treatment indications and subsequently, no AST interpretations can be provided by the clinical microbiology laboratory. The establishment of relevant, accurate, and reproducible *in vitro* susceptibility data for pathogens not covered by the agent's intended use could provide valuable additional data for clinicians to consider in the context of MDROs with very few treatment options. 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 antimicrobial powders to develop new AST devices. Currently, there are barriers in obtaining agents under investigation as new drugs that impede test development between approval of new antimicrobial agents and availability of a corresponding AST device. To help bridge this gap, IDSA recommends that FDA require pharmaceutical companies make new antimicrobial compounds available to select clinical laboratories and research reference laboratories with expertise to develop reference broth or agar dilution minimal inhibitory concentration (MIC) tests according to Clinical & Laboratory Standards Institute (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 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 also recommends that FDA

revise AST acceptance criteria to align with International Organization for Standardization ISO) Standard 20776-2 (Clinical Lab and IVD Test Systems – Susceptibility Testing of Infectious Agents & Evaluation of Performance of AST Devices – Part 2: Evaluation of Performance of AST Devices). This ISO standard provides a protocol for doing repeat testing that is also very beneficial in reducing the impact of reference testing variability and lack of reproducibility.

Another alternative would be to have pharmaceutical companies provide Epsilometer (E-)test strips to all hospitals until such time that a corresponding AST device is approved. Current pharmaceutical company supplies of E-test strips are limited, thus depriving patients of access to rapid results in the often 3-5 year gap between drug and device approval. IDSA urges FDA to strike an appropriate balance on this issue, and we would be pleased to provide experts to work with FDA to develop criteria for clinical laboratories that are capable of proving results on newly-approved antimicrobial agents to physicians via standard Clinical & Laboratory Standards Institute (CLSI) AST reference methods.

A Look Ahead

IDSA lauds FDA efforts to address the challenges of AST development and we hope the agency will adopt our recommendations to further strengthen the 2016 draft guidance. As required by the 21st Century Cures Act, we appreciate that the FDA is now permitted to review breakpoints updated by external standards organizations such as CLSI, and we look forward to the forthcoming December implementation of an FDA website for interpretive criteria. When breakpoints require revision based upon new clinical data that were not available at the time of the original approval, we also encourage the FDA to provide a similar path for device manufacturers to update breakpoints for older agents on devices.

IDSA recognizes that additional work will be necessary to comprehensively stimulate the inclusion of new antimicrobial agents on AST devices. As FDA works with other stakeholders and Congress on this issue, we urge you to consider the following opportunities for progress.

Clinical Trials Network(s) to Reduce Time and Costs Associated with AST Development

Greater efficiencies in clinical trials could help reduce the time and the 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. Early detection of resistance remains central to limiting transmission. For example, a recent mathematical modeling study[1] indicated that proper use of rapid susceptibility testing could limit the spread of antibiotic resistance in gonorrhea and delay the overall resistance for several years. Findings such as these are particularly important for resistant pathogens with limited treatment options available, and also provide the needed time for development of new therapies.

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. Additionally, earlier and increased interaction with the Agency to develop reasonable standards and guidelines for new or significantly revised technologies is a

[1] Tuite et al. "Impact of rapid susceptibility testing and antibiotic selection strategy on the emergence and spread of antibiotic resistance in gonorrhea". *J Infect Dis* 2017.

critical step in maintaining up-to-date access to AST devices. Alternatively, FDA interactions with trade organizations such as AdvamedDx could also provide a mechanism for early and frequent industry input into such guidance.

Economic Incentives

Lastly, IDSA remains concerned that the development of AST devices is costly, and that insufficient financial incentives exist for developers to bring quickly these tests to market. 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 greater risk. However, this early development is essential to close the gap between the availability of a new antimicrobial agent and the ability to provide susceptibility data. 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 incent the co-development of AST devices.

Innovation and Emerging Technologies

New technologies have appeared that allow the use of novel methods for the identification and susceptibility testing of bacteria. A major constraint for laboratories is the ability to migrate from existing methods, many of which have been established over decades of testing, to new technologies which show promise but often require significant investments. IDSA recommends increased collaboration between FDA, in vitro diagnostics (IVD) manufacturers, and committees like the CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) to establish equivalency guidelines that accelerate use of new technologies. Device manufacturers are currently operating with a limited number of guidelines to establish equivalency between existing methods and new technologies that discourages investment in innovation. An initial step could be to pilot select new technologies with the FDA, working closely together along the R&D pathway to accelerate the introduction of these innovations into the market.

Once again, IDSA thanks FDA for soliciting input from the diagnostics community and promoting the timely development of AST devices. These tests are vital for providing high-quality patient care and an essential component of broader efforts to fight antimicrobial resistance. We look forward to continuing to work with the FDA and other stakeholders on this important issue.

Sincerely,

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