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Re: Concept Paper: Advancing Regulatory Science for Highly Multiplexed Microbiology / Medical Countermeasure Devices [FDA-2011-N-0557]

To whom it may concern:

The Infectious Diseases Society of America (IDSA) is pleased to have this opportunity to comment on the U.S. Food and Drug Administration's (FDA) concept paper, "Advancing Regulatory Science for Highly Multiplexed Microbiology/ Medical Countermeasure (MCM) Devices". Our comments and recommendations below address the clinical and public health need for better infectious diseases diagnostic devices, clinical considerations for device design, and key issues for device validation.

IDSA represents nearly 10,000 infectious diseases physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases (ID). The Society's members focus on the epidemiology, diagnosis, investigation, prevention and treatment of infectious diseases in the United States and abroad. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, surgical infections, other life-threatening infections caused by unusual or drug-resistant microorganisms, and new and emerging infections, such as severe acute respiratory syndrome (SARS) and H1N1 influenza.

Clinical and Public Health Need

IDSA applauds the FDA for taking this initial step towards the development of better diagnostics for a range of infectious diseases. The FDA concept paper presents options being considered for the performance validation of highly multiplexed microbiology/MCM devices, defined by FDA as "those that are nucleic acid-based and intended to simultaneously detect and identify a large number of organisms (≥20) using a single, direct clinical specimen." FDA has sought to address many of the challenges inherent in the development and clinical interpretation of these devices, including a potentially large number and volume of clinical specimens for detecting many more pathogens, and the risk of false positives presented by testing for low prevalence pathogens.

The value of improved ID diagnostic devices is undeniable. Multiplexed diagnostic devices, in particular, will be essential for responding to a range of clinical and public health needs, including detection of a bioterrorist event or other public health emergency. Many infections currently go undiagnosed and are treated empirically. Clinicians often do not have diagnostics with good sensitivity for the specimens they can readily obtain, or they need to make clinical decisions before data are available. Empirical treatment has led to the widespread overuse of antibiotics, antivirals and other antimicrobials, increasing the problems of multidrug resistance and antimicrobial-related adverse events, ultimately driving up the cost of healthcare. The development of more accurate, simple and reliable diagnostic technologies will improve disease diagnosis and antimicrobial stewardship. Molecular diagnostic tests will enable the use of smaller volume samples and possibly less invasive samples, (e.g., a nasopharyngeal swab instead of a bronchoalveolar lavage), improving patient comfort while providing an accurate diagnosis. Better diagnostic tests will improve our understanding of etiology and pathogenesis of a range of infections, including co-infections, and foster better patient management by targeting appropriate therapies and enabling the monitoring of microbiologic responses to treatment.

Clinical Considerations for Diagnostic Device Design

IDSA supports the development of multiplexed diagnostic devices because multiplexed devices simulate how physicians think about diagnosing patients, in terms of clinical syndromes. We support the development of syndromic panels, e.g., a panel for diarrhea and a panel for respiratory infection. It is also important that each panel account for various clinical characteristics that complicate diagnosis and treatment, such as immunocompetent vs. immunocompromised; age—adults, pediatric, and neonatal; geographic location; and other contributing factors such as travel, pets, and occupational exposure. IDSA recommends that the FDA advises diagnostic companies to consult with clinical infectious diseases experts in the design of diagnostic panels. Analytical and clinical validation of devices is critical, and because syndromic panels may be used for different types of specimens, tests may have to be validated on more than one specimen type.

Tests should be designed in a way that takes into account and aids clinical interpretation during normal clinical use and during public health emergencies. The FDA has expressed concern about the risk of a false positive diagnostic result for low prevalence analytes, including MCM targets. We believe that the chance of obtaining a false positive can be decreased through device validation (see below), but it cannot be completely eliminated. However, clinicians manage the final diagnosis by putting the diagnostic result into the clinical context. Communication with and confirmatory testing by public health authorities may also be required, helping to manage the risks of prematurely declaring a health emergency. The FDA is considering the benefits and risks of reporting test results as "For Information Only", (e.g., for resistance markers, in the context of infection control for hospital surveillance). While this is an interesting idea, it has the potential of adding confusion to clinical interpretation, especially when you consider the variety of physicians who may be receiving this information (e.g., ID specialists, generalists, public health practitioners).

Another issue that complicates clinical interpretation is understanding colonization versus infection. For example, an organism such as *Streptococcus pneumoniae* may colonize the respiratory tract as well as cause clinical disease. Quantitative data may help to distinguish between colonization and infection, but relative quantification may be adequate. Current culture data are reported in a semi-quantitative manner, for example: rare, scant, moderate, or many; such

a semi-quantitative approach may also be adequate with multiplexed molecular tests. Quantitative assays may be an unnecessarily high bar for developers of these molecular tests and may not significantly improve clinical diagnosis. Finally, until there are international standards for accurate quantification, the FDA could facilitate consensus-building around a set of standards by engaging with appropriate societies and other organizations.

Diagnostic Device Validation

Validation is a critical process in the development of better diagnostic devices. A balance should be achieved between meeting the clinical need for improved diagnostics and assuring that device performance meets appropriate standards. IDSA applauds the FDA for not simply applying the clinical validation approach used for single analyte devices to multiplexed devices, which would result in a significantly larger number of clinical specimens and a prohibitively large volume of specimen needed for studies. We appreciate the creative approach described for comparator methods in the proposed concept, which will make clinical trials more feasible. Flexibility is needed for the comparator; it would not be appropriate to use culture as the comparator for pathogens that do not grow well, but sequencing amplicons could be used, for example.

For determination of clinical sensitivity, the use of banked specimens and at times spiked specimens will be very valuable. Having these alternatives for positive samples will be especially important for low prevalence pathogens (e.g., *Listeria*, *Neisseria*, and *Brucella*) and infections that are more common outside the U.S. (e.g., dengue and malaria). For rare pathogens, the clinical sensitivity studies may be performed predominately on banked and spiked specimens, with the clinical specificity studies done on a larger sample size of prospectively collected samples, to decrease the chance of a false positive result. With regard to sample matrices, syndromically relevant matrices should be tested (e.g., cerebrospinal fluid, blood, respiratory, stool for meningitis/encephalitis) and depending on the pathogen, specimen types from the same anatomic "compartment" could be considered equivalent and be pooled during the device analytical evaluation. An *in silico* approach would be very valuable for assessing analytical specificity and can be particularly helpful for rare pathogens or rare subtypes of pathogens (e.g., less common *Klebsiella* species). Finally, it will be important to design a flexible system so that when a new target needs to be added, the entire panel does not need to be clinically validated. Ideally the interactions of the new primers/probes could be assessed by an analytical evaluation, possibly including an *in silico* component, with the clinical validation needed only for the new target.

Thank you for the opportunity to comment on this concept paper for development of multiplexed microbiology/MCM diagnostics. Should you have any questions about these comments, please contact Audrey Jackson, PhD, IDSA's senior program officer for science and research, at ajackson@idsociety.org or 703-299-1216.

Sincerely,

Thomas G. Slama MD

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President