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Infectious Diseases Society of America

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[By Electronic Submission to www.regulations.gov]

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

Re: Comments on Docket No. FDA-2011-D-0360; Draft Guidance for Industry and Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

Dear Sir/Madam:

The Infectious Diseases Society of America (IDSAs) is pleased to offer comments on the draft guidance, "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)." We recognize that the Food and Drug Administration (FDA) is committed to protecting patients and look forward to continuing our work with the agency.

Over the past several years, IDSAs has stressed the importance of innovative diagnostic devices for the care of patients suffering from infectious diseases (ID), most notably in our 2013 report, [Better Tests, Better Care: Improved Diagnostics for Infectious Diseases](#). Improved diagnostics can allow physicians to rapidly identify the pathogen infecting a patient and prescribe the most appropriate treatment, increasing the likelihood of a positive patient outcome. Notably, high quality ID diagnostics have a unique ability to protect the broader public health by alerting health officials of the need to trigger protocols to contain outbreaks and prevent the transmission of infections.

IDSAs recognizes that there are valid concerns about the risks associated with LDTs in areas such as cancer, genetic testing, as well as infectious diseases. While many ID LDTs have a long history of safe and effective use in patient care, other ID LDTs may not have been evaluated as rigorously. Nonetheless, IDSAs believes the risks raised by the use of ID LDTs are dwarfed by their advances and benefits to patient care. Unlike other disease areas, the evidence that the ID LDTs provide unreliable results that lead to harmful patient care decisions is lacking.

IDSAs is very concerned that LDT oversight, as currently proposed by the Food and Drug Administration (FDA), could impede patient access to existing high quality or state of the art tests and threaten needed innovation in the development of novel tests for constantly changing and emerging infectious diseases. While smaller clinical microbiology laboratories may be only modestly impacted by this regulation because they currently use few or no LDTs, other microbiology laboratories, particularly those in major medical centers, have literally dozens of LDTs that will be subject to oversight. These medical centers specialize in transplantation medicine and management of complex critically ill patients, and they rely on LDTs to provide the highest level of care. However, these same

laboratories lack the resources, both financial and administrative, for even a single 510(k) submission, let alone submissions for all tests. For LDTs that are classified as high risk, these laboratories will almost certainly be unable to navigate the complex, costly premarket approval (PMA) process.

In the face of these challenges, IDSA believes that many clinical microbiology laboratories, especially in leading US medical centers that provide high quality advanced specialized care, will choose to stop using LDTs entirely, and either move to available commercial diagnostic tests or send testing to outside reference laboratories, both of which have considerable disadvantages. For example, commercial assays are not yet available for the entire range of testing currently covered by LDTs. Those tests that are available are often more expensive and may require investment in new instruments from multiple companies, as no one company has the entire menu of tests that are currently covered by LDTs.

Most importantly, sending clinical specimens to reference laboratories for testing will significantly increase the turnaround time required to get the results to physicians. Rapid diagnostics that facilitate early initiation of life-saving treatment are critical in infectious diseases patient care, where even a few hours delay can significantly impact patient outcomes. Public health responses also require rapid identification of an emerging health risk, and any delay in activation of important public health protocol allows dangerous infections to spread. Delays incurred by sending specimens to reference laboratories with inflexible testing schedules may significantly impact detection of outbreaks of infectious diseases.

IDSA would like to offer several specific recommendations on the proposed regulatory framework below.

Prioritization and Classification of risk

The classification of risk of LDTs is a critical area of the proposed regulatory framework. IDSA recommends that the FDA consider past and present uses of LDTs, recognizing different patterns of use in different disease areas, and noting both benefits that LDTs contribute to patient care as well as their potential harm. The FDA should balance the risk associated with current use of LDTs in each relevant disease area against the risk of curtailing patient access to LDTs under the proposed regulations. Given the importance of this process, **IDSA would like to offer its member expertise to serve on the FDA's review panels to classify LDT risk. Furthermore, IDSA would be pleased to help convene experts to poll literature and other sources of information to identify tests that have appropriate information that establishes their safety and clinical validity.** Such a mechanism would limit the need of laboratories to undertake duplicative efforts to demonstrate clinical utility that has already been proven.

In its regulatory framework, the FDA has prioritized oversight of high risk LDTs for “certain infectious diseases with high-risk intended uses,” notably viral load tests for cytomegalovirus. These LDTs for cytomegalovirus have been in use for many years by laboratories, with well-documented data demonstrating clinical validity and peer reviewed literature supporting their use. These LDTs have become the standard of care. Given their longstanding use and significant supporting data, **IDSA asserts that tests for transplant-related viruses do not pose a high risk to patients and should be reclassified as moderate risk tests. IDSA offers the expertise of its members to assist in this process.**

Currently the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendment (CLIA) regulations require that LDTs are analytically validated. Therefore, if clinical validity is demonstrated by a similar commercial high risk test, clinical microbiology laboratories should not be required to re-demonstrate this via costly PMA submission. **IDSA also urges the FDA to allow LDTs that are high risk to be compared to high risk approved devices as predicates.**

Definition of healthcare system for oversight exemption

While IDSA applauds the FDA's carve outs for oversight exemptions, we are concerned the restrictions that preclude the testing of patients being treated at a healthcare facility outside of the laboratory's healthcare system will adversely impact ID patient care. In many areas, a large institution's clinical microbiology laboratory may serve as a regional reference laboratory to hospitals outside of its system, providing not only a quick turnaround time for tests, but also consultations to discuss laboratory results to ensure appropriate clinical care decisions are made. The FDA's current definition of a healthcare system precludes oversight exemption for this use of LDTs. **IDSA urges the FDA to modify the definition of healthcare system to include instances where local, but non-system, healthcare institutions interact to provide diagnostic testing and expertise.**

LDTs definition of rare disease

For the purposes of diagnostic tests, FDA currently defines rare diseases as those that are tested for no more than 4000 times each year nation-wide. Rare infectious diseases present some unique challenges to the FDA's current definition. Rare infections, such as encephalitis caused by herpes simplex virus (HSV) and varicella zoster virus (VZV), or invasive aspergillosis have symptoms that are also common in more widespread infections. In order for these rare infections to be ruled out, they must be tested for at far higher rates than the FDA limit of 4000/year nationwide.

The Center for Drug Evaluation and Research (CDER) at the FDA defines rare diseases, based on the 1983 Orphan Drug Act, as those that affect fewer than 200,000 patients nationwide. **IDSA proposes that the LDT regulatory framework align with this definition to permit continued enforcement discretion for LDTs for diseases with fewer than 200,000 patients in the United States, not by the number of tests performed.** In addition, pathogens can cause both common and rare diseases; for example, herpes encephalitis is a rare disease, while genital herpes infection is much more common. **IDSA recommends that the FDA not constrain its definition of a rare disease based on the pathogen, but rather on the disease itself.**

Traditional LDTs

The Draft Guidance states that FDA intends to continue to exercise enforcement discretion with respect to premarket review requirements for "Traditional LDTs". The Draft Guidance lists four factors that FDA intends to consider in determining whether to exercise enforcement discretion. Number (4) is "Whether the LDT is interpreted by qualified laboratory professionals, without the use of automated instrumentation or software for interpretation." IDSA points out that the term "automated instrumentation" is not well defined, especially in light of the fact that modern laboratory instrumentation in general is increasingly automated. Likewise, the phrase "use of software for interpretation" is also poorly defined, with software being a ubiquitous component

of modern laboratory testing. **IDSA recommends the FDA clarifies these definitions to ensure no confusion on what tests meet the “traditional LDT” criteria.**

LDTs for unmet needs

For LDTs that address unmet medical needs, IDSA has concerns over the regulatory framework the FDA has proposed when a commercial test meeting this need is approved. **IDSA does not believe the 12-month period laboratories are given to submit to the FDA or switch to the commercial test is sufficient, and recommends at least a 2-year phase-in period.** Most clinical microbiology laboratories operate under a 12-month capital upgrade cycle, and depending on when a commercial test is approved, would not likely be able to purchase the equipment needed for a test within the 12-month period, resulting in situations where laboratories may lose the capability to conduct any testing for critical unmet medical needs.

IDSA also urges the FDA to delay regulatory oversight of LDTs for unmet medical needs until several (two or more) commercial tests are approved. With only one option, laboratories may be forced to purchase expensive equipment that may be used for only one test. Delaying regulatory oversight of LDTs for unmet medical needs until several commercial tests for the unmet medical need are approved will give laboratories much needed flexibility to choose tests appropriate to their space and cost limitations. Moreover, while the vast majority of FDA-approved and cleared tests have excellent performance characteristics, there are clear instances of tests that identify viral resistance mutations in which LDTs have superior performance characteristics compared to commercial tests. Delaying enforcement until multiple commercial tests are approved will assist laboratories in addressing these issues.

The FDA has indicated that, if a commercial test is used on a specimen other than what was originally intended, that test would be considered an LDT subject to oversight. **IDSA argues that the need to test these non-intended specimens represents an unmet medical need.** For example, if a commercial diagnostic test can identify a given pathogen in serum, but there exists a need to test cerebrospinal fluid (CSF) for the same pathogen, the laboratory should perform an analytical evaluation using CSF specimens and the use of an analytically verified LDT to test CSF for this pathogen should be subject to enforcement discretion.

Finally, when manufacturers make improvements to tests, the process that has been created to speed the clearance of the modified test is extremely important to improving access to testing. For example, when adding an emerging pathogen to a multiplexed test, it is expected that a comprehensive analytical validation will be completed. **Allowing a more limited clinical trial to be performed focusing on the new pathogen would make the test available to clinical laboratories in a more rapid manner.** Given how rapidly pathogens emerge and evolve, lack of frequent updates is particularly problematic in the area of infectious diseases and a key factor in the need for continued flexibility in this disease area.

LDTs that rely on non-FDA approved databases

Many LDTs use a commercial platform and specimens as intended, but use validated databases not approved by the FDA for results. Examples include sequencing platforms used to identify human immunodeficiency virus (HIV) drug resistance and Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) systems for bacterial and fungal identification. Over the course of testing, specimens regularly contain new sequences that are not contained in the

FDA-approved database. Moreover, as use of MALDI-TOF expands, databases often lag behind the diverse array of bacteria encountered in the clinical microbiology laboratory.

IDSA requests that the FDA clarify the LDT regulatory oversight of laboratory testing that rely on non-approved databases. Laboratories should be able to construct and consult their own database, or turn to independent databases to identify and verify their sequence or proteomic information. **IDSA recommends that the FDA propose a simple, straightforward regulatory mechanism to allow validation and unhindered access to databases other than FDA-approved options.**

LDTs exemption from user fees

If clinical microbiology laboratories are forced to pay user fees during submission of tests, this will add another severe burden that will hinder patient access to testing. Moreover, these higher costs of testing would likely be passed on to patients, increasing healthcare costs. **IDSA strongly urges that the FDA extend the exemption beyond 2017.**

Outreach and Education for Clinical Microbiology Laboratories

As the agency moves forward in implementing its oversight of LDTs, IDSA stresses that the majority of clinical microbiology laboratories have never interacted with the FDA. It is critical that the FDA implement a highly robust mechanism to conduct outreach and education on FDA regulations and processes for these individuals to provide them with the necessary information, guidance and assistance to navigate FDA's regulatory processes and continue to provide needed, high quality testing services.

IDSA hopes these comments are useful to the FDA as the agency moves forward in their efforts to develop regulatory oversight of LDTs. LDTs are important in infectious disease diagnostics, and serve an essential, often vital, purpose. While commercial assays are available for some pathogens and disease states, they are not available for all, and even available commercial assays may be too expensive for many laboratories. Many LDTs are already utilized under a system of regulations by CAP and CLIA that require validation. There may be opportunities to enhance assessment of LDTs through CLIA which may ultimately be effective and pose less risk of limiting access to testing.

Infectious Diseases LDTs exemplify bench to bedside innovation that allows patients, and their physicians, access to “cutting edge” quality enhancements in patient care. Hopefully, FDA oversight activities will facilitate the ever-changing needs of timely test development.

Should you have any questions or concerns about these comments, please feel free to contact Greg Frank, PhD, IDSA Program Officer for Science and Research Policy, at gfrank@idsociety.org or 703-299-1216.

Sincerely,



Stephen B. Calderwood, MD, FIDSA
IDSA President

About IDSA

IDSA represents over 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin-resistant enterococci (VRE), and Gram-negative bacterial infections such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and, finally, emerging infections such as Ebola virus, enterovirus D68, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and bacteria containing the New Delhi metallo-beta-lactamase (NDM) enzyme that makes them resistant to a broad range of antibacterial drugs.