April 27, 2016

Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Ave., Bldg. 1, Rm. 2217
Silver Spring, MD 20993

Dear Commissioner Califf:

The Infectious Diseases Society of America (IDSA), the American Society for Microbiology (ASM), and the Pan American Society for Clinical Virology (PASCV) recognize that the Food and Drug Administration (FDA) is committed to protecting patients. Our societies have closely followed the FDA's draft guidance proposing to regulate laboratory developed tests (LDTs), and are deeply concerned that the regulations will negatively impact the care of patients being evaluated for infectious diseases (ID).

The proposed regulations, developed primarily out of concerns over oncology and genetic testing, will have wide reaching impact on all clinical laboratories. Our societies are concerned that ID LDTs, which have little evidence of providing unreliable results that lead to harmful patient care decisions, are not being appropriately considered by the FDA's proposed regulations. Many ID LDTs have a long history of safe and effective use in patient care, and our societies firmly believe the risks posed by ID LDTs are dwarfed by their advances and benefits to patient care. In early 2015 IDSA, ASM, and PASCV submitted comments to the FDA's draft guidance. With the final guidance release imminent, our societies wish to again highlight the unique concerns surrounding ID LDTs. We have attached a position paper recently published in *Clinical Infectious Diseases* with recommendations designed to help minimize the disruption of LDTs in the care of patients suffering from infection.

Time is of the essence in ID patient care, where even a few hours delay can negatively impact a patient's outcome. To rapidly administer appropriate treatment for infectious illness, physicians rely on laboratories to provide clinically relevant diagnostic test results, both commercial *in vitro* diagnostics (IVDs) and LDTs, to not only identify the cause of infection but also guide therapeutic selection. Timely local testing is especially important at major medical centers specializing in transplantation and the management of complex, critically ill patients. Here, physicians and clinical laboratory scientists also regularly develop LDTs to keep pace with newly emerging diseases. ID diagnostics also play a critical role in the public health response to outbreaks, hospital infection prevention, and the stewardship of antimicrobial drugs to limit the development of drug resistance.

IDSA, ASM and PASCV support the need to ensure that LDTs are safe and effective tools for the management of patients. However, we remain extremely concerned that the barriers created

by the proposed regulations will impede patient access to high quality ID LDTs. The review requirements, designed for tests manufacturers, will create an impossible challenge, both in financial and administrative resources, for routine clinical laboratories; a laboratory would likely be unable to undertake a single moderate risk 510(k) submission, let alone navigate the high risk premarket approval (PMA) process. The resource burden would likely force many laboratories to discontinue developing innovative LDTs and either move toward exclusive use of commercial IVDs or send testing to outside reference laboratories. Below, we present three examples where loss of local and timely LDT testing due to FDA oversight would negatively impact the care of patients with serious infections.

1: Testing of newborns for disseminated herpes simplex virus (HSV) infection
Disseminated HSV infection in newborns is a life threatening disease, associated with high morbidity and mortality. Rapid diagnosis and treatment is critical in halting disease progression. Many clinical laboratories have developed and comprehensively validated PCR LDTs to test cerebrospinal fluid (CSF) and blood of these newborns for swift, local testing. While rare, test volume exceeds the FDA draft guidance's 4000/tests nationwide threshold for the rare disease testing exemption. Two FDA cleared commercial tests for HSV CSF analysis are available, but require purchase of an instrument for the sole use of this test. There are currently no FDA cleared assays to test blood. Clinical laboratories are unlikely to commit limited resources to purchasing the instrument due to the low frequency of the disease. This could create a significant loss of patient access to the local, rapid testing needed to combat neonatal HSV infection.

2: Identification of opportunistic viral infection in transplant patients
The FDA draft framework prioritizes oversight of high risk LDTs for "certain infectious diseases with high-risk intended uses," notably viral load tests for cytomegalovirus, and possibly Epstein-Barr virus and BK virus. These, and other viruses, represent a major risk for serious infections in immunocompromised transplant patients, where LDTs play a critical role in the longitudinal monitoring for viral reactivation. These LDTs have been in use for many years by clinical laboratories, with well-documented data and peer reviewed literature demonstrating clinical validity. In many cases, these LDTs have become standard of care. Should these tests be classified as high risk, clinical laboratories would be unable to bear the enormous cost of a PMA submission. This would likely lead to a situation where few local testing options exist to guide the care of these patients; it could also lead to unacceptable delays in time to diagnosis as samples are sent out to commercial reference laboratories.

3: Rectal and pharyngeal screening of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*
Chlamydia trachomatis and *Neisseria gonorrhoeae* are among the most frequently reported communicable diseases in the U.S. In particular, *N. gonorrhoeae* is increasingly difficult to treat due to the development and spread of antimicrobial resistant strains and is specifically addressed in the President's combating antibiotic resistant bacteria (CARB) initiative. Rapid identification and treatment will improve patient outcomes. The 2015 Centers for Disease Control and Prevention (CDC) sexually transmitted disease (STD) guidelines state that rectal and pharyngeal screening for these pathogens must be performed by nucleic acid amplification testing (NAAT). Urogenital specimens are the only approved sources for the currently available FDA-cleared NAAT IVDs, forcing clinical laboratories to modify these tests for rectal or throat specimens. The FDA draft guidance indicates that a commercial test used on a specimen other than what was

originally approved would be considered an LDT subject to oversight. As stated above, clinical laboratories would be unable to complete a 510(k) submission for this new test, and would likely cease testing, and therefore limit patient access to these critical LDTs.

Both LDTs and commercial tests play important roles in the care of patients with infectious diseases. IDSA, ASM, and PASCV reiterate that economic incentives and appropriate regulation for both types of diagnostics are needed to ensure that patients—and their physicians—have access to cutting edge quality laboratory diagnostics. As stated in our attached policy position letter, our societies are willing to work with the FDA to develop equitable and data-driven oversight policies for ID LDTs. Our societies hope the final FDA oversight activities will facilitate, and not impede, the ever-changing needs of timely ID test development.

Sincerely,

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