The Honorable Larry Bucshon, MD
United States House of Representatives
1005 Longworth House Office Building
Washington, DC 20515

The Honorable Diana DeGette
United States House of Representatives
2111 Rayburn House Office Building
Washington, DC 20515

Dear Representatives Bucshon and DeGette:

The Infectious Diseases Society of America (IDSA) and the American Society of Transplantation (AST) appreciate the opportunity to offer feedback on the draft Diagnostic Accuracy and Innovation Act (DAIA) and corresponding August 3 Food and Drug Administration (FDA) technical assistance document. Notably, we look forward to sharing our perspectives on the important role of laboratory developed tests (LDTs) in transplant and infectious diseases (ID) medicine and the care of complex, critically ill patients, as well as the potential effects of proposed regulations on innovation and patient access to testing.

LDTs have been successfully used for decades in the diagnosis of infections such as cytomegalovirus (CMV). CMV is a common infection in patients receiving organ and bone marrow transplants. Molecular CMV viral load testing provides substantially faster and more sensitive diagnostic testing than the older method of culturing the virus from blood samples. Requiring that these LDTs be submitted to the same FDA premarket approval protocol as commercial tests would force academic medical centers and hospital laboratories to undertake an unaffordable and inappropriately burdensome process for which they could not recoup the costs. As a result, many of these tests would not be performed, or would be outsourced to reference laboratories, causing delays that would directly impact patient care. Such delays are often critical, meaning the difference between life and death in infectious disease treatment. The scenario would set back transplant medicine, where LDTs have become the standard of care, by 20 years and cause undue, devastating harm to patient care. Given the background of existing and well-established validation and quality assurance and accreditation programs for LDTs, our Societies propose that FDA and CMS utilize the expertise of the professional societies to permit continued safe performance of critical LDTs in organ transplantation and hematopoietic cell transplantation.

We appreciate your close attention to this multifaceted issue and look forward to working with you to craft appropriate policies that spur desired innovation and protect patient access to high-quality care.

How laboratory developed tests are used in transplant medicine

The field of organ transplantation cannot provide swift, accurate patient care without ready access to laboratory diagnostic tests, many of which are locally developed and standardized. Examples include defining immunologic acceptability of donor and recipient pairs at the time of transplantation (histocompatibility), monitoring for donor-specific antibody after transplantation,

and examining tissue and blood for viral infection and rejection in the presence of graft dysfunction.

To rapidly administer appropriate treatment for infectious illnesses, physicians rely on laboratories to provide clinically relevant diagnostic test results that identify the cause of infection and guide therapeutic selection. In-house testing is essential at major medical centers that specialize in transplantation and the management of complex, critically ill patients, where physician and clinical laboratory scientists regularly develop and validate LDTs to keep pace with newly emerging diseases and offer diagnosis of less common pathogens that do not have FDA-approved commercial testing.

There are few commercial entities providing FDA-cleared assays for histopathology and histocompatibility testing. In the United States alone, more than 30,000 solid organs, over 8,000 hematopoietic stem cell transplants, and more than 30,000 searches for stem cell donors (overseen and regulated by the National Marrow Donor Program), all requiring histocompatibility testing and histopathology assessment, are being performed each year. There are currently more than 114,000 patients on the national transplant waiting list, including more than 95,000 patients awaiting kidney transplantation, and over 19,000 patients waiting for lifesaving heart, liver, and lung transplants. Enforcement of the current proposed regulations and the exclusion of histopathology and histocompatibility testing from premarket review exemption criteria would jeopardize transplantation in the United States.

Equally important are the assays currently used to follow patients after transplantation for infectious complications. Infections are a significant cause of morbidity and mortality after solid organ transplantation. The majority of the assays for prevention, diagnosis, and treatment monitoring of common infectious complications employ nucleic acid assays for herpesviruses and polyomaviruses developed by individual institutions. Commercial FDA-licensed assays for these analytes are unavailable. Transplant recipients are susceptible to unusual and rare pathogens that are sometimes only detectable using in-house-developed assays performed in a CLIA-approved laboratory setting. Accordingly, restrictions imposed on the performance of these assays would seriously jeopardize the ability of physicians to care for patients after transplantation.

The transplant and ID communities are fully aware that standardization and quality assurance for these diagnostic assays are crucial. Laboratories in academic and established reference laboratories only permit use of in-house tests that have been sufficiently validated against clinical samples. Federal regulations for the implementation of CLIA already require analytical validation of all assays used by a laboratory. In turn, this requires establishing performance criteria, evaluating the performance of a laboratory assay vis-à-vis those criteria, establishment of a quality control program for ongoing evaluation of test performance, and a technologist training protocol.

Transplant ID concerns regarding draft DAIA and FDA approach

The FDA technical assistance document proposes a regulatory paradigm for *in vitro* diagnostics that departs significantly from DAIA. If enacted, prohibitive requirements for academic and hospital-based laboratories will severely impact public health and devastate ID patient care,

particularly transplant medicine. The current DAIA draft is also not a consensus document, and it appears to give priority to market-based incentives for commercial test manufacturers and the largest reference laboratories over a goal of providing optimal patient care.

FDA has specifically proposed excluding *in vitro* clinical tests used for HIV testing and transplant patients, which would include tests for CMV and viral load testing for Epstein-Barr, BK virus, HHV6, adenovirus, and others from the precertification pathway. The rationale for these exclusions is unclear and in opposition to the risk-based framework of the document. The FDA recommendation is a major concern in light of the prohibitive costs of premarket submissions and potential impacts on innovation and patient care.

LDTs for transplant viral load testing have been in regular use for decades, with well-documented data demonstrating clinical validity supporting their use in peer-reviewed literature. In many cases, these LDTs have become the standard of care. Their use is recommended in many professional guidelines. It is critical to note that tests for serious or life-threatening infectious diseases may only carry moderate risk, which was allowed under previous drafts in the definitions of risk. Our Societies have long advocated that LDTs with proven safety, efficacy, and validity data – such as transplant viral load tests – should be included in any legislative exemption language. In 2016, the FDA Microbiology Panel of the Medical Devices Advisory Committee proposed that transplant viral load tests be down-classified from Class III to Class II, or moderate risk. We urge FDA to complete the down-classification process as soon as possible to increase opportunities for developmental innovation and ensure that these tests are removed from high-risk consideration and eligible for proposed precertification pathways.

Our Societies agree that a precertification pathway for institutions and groups of similar tests may help ease the prohibitive burdens of premarket review for many developers, including academic medical centers and not-for-profit laboratories. However, we are deeply concerned that FDA proposes a caveat singling out transplant tests as ineligible for precertification. This blanket prohibition would disproportionally affect diagnostics for infectious diseases that have long been safely and effectively used to improve patient outcomes while ignoring other areas of medicine where high-risk LDTs have documented concerns.

Further, these caveats are without scientific justification and delegitimize the risk-based core of the FDA proposal by banning arbitrary categories of tests without reviewing validation data. Removing the precertification option for transplant-associated virus viral load testing – an area where LDTs for infectious diseases are most needed – would have devastating effects on patient care that would ripple out to various other areas of medicine affected by transplant ID. Multiple studies have demonstrated that rapid institution of appropriate therapy for infectious diseases improves patient outcomes and decreases morbidity and mortality. If these tests fall out of the precertification category, even large reference laboratories will not be able to keep pace with demand. Additionally, there is no evidence that commercial tests for these viruses (where they exist) are better or safer than tests designed in clinical laboratories.

IDSA and AST remain concerned that the current FDA proposal to regulate LDTs and IVDs as a single category of tests will negatively affect public health and patient care for transplant medicine and infectious diseases. It is imperative that any legislation on this complex issue

reflect balanced input from diverse stakeholders, including physicians in transplant ID. Most importantly, it should serve the best interests of patients who need access to safe and rapid testing. We appreciate Congress' ongoing commitment to patient care and public health and your willingness to engage with stakeholders on this complex issue. We hope there will be additional opportunities to provide expertise and work together to craft appropriate policies that spur innovation while protecting patient access to high-quality diagnostic testing.

Sincerely,

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President, IDSA

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President, American Society of Transplantation

IDSA represents over 11,000 infectious diseases (ID) physicians and scientists devoted to patient care, prevention, public health, education, and research in the field of ID. Our members care for patients with or at risk of serious infections such as HIV, hepatitis C virus (HCV) and infections caused by antimicrobial resistant pathogens, and are on the front lines of responses to public health emergencies such as Ebola virus, Zika virus, MERS-CoV, and influenza.

Founded in 1982, the American Society of Transplantation (AST) is an organization of more than 3,600 professionals dedicated to advancing the field of transplantation and improving patient care by promoting research, education, advocacy, and organ donation. The society is the largest transplant organization in North America and is recognized as the premier society for transplantation. AST members are sought out as transplant experts and advocates for guidance, research, and resources related to transplantation.