AMERICAN SOCIETY OF TRANSPLANTATION (AST)
POSITION ON
FDA REGULATION OF LABORATORY-DEVELOPED ASSAYS

The Food and Drug Administration (FDA) has recently published a framework for regulatory oversight of Laboratory-Developed Tests (LDT) in the form of a draft guidance document (Federal Register/Vol. 79. No. 192/Friday, October 3, 2014/Notices). There are provisions for a 90 day written comment period followed by a public meeting for verbal comments scheduled for January 8th and 9th, 2015.

The impact of the proposed regulatory burden on transplantation centers will be substantial. The AST offers the following comments on sections of the guidelines that are pertinent to the practice of solid organ transplantation:

1. Class III, High Risk LDTs: These include (a) LDTs with the same intended use as a cleared or approved companion diagnostic, (b) FDA-approved Class III medical devices, (c) diagnostic devices of certain infectious diseases with high-risk intended uses, (d) LDTs used to screen for serious diseases in asymptomatic patients with no other available confirmatory diagnostic product, and (d) LDTs to determine the safety of blood or blood products.

   LDTs in this category LDTs will be subject to all registration/listing, manufacture reporting, premarket review, and quality system regulations envisaged in the draft guidance document.

   Position of AST: The AST represents the interests of more than 100,000 patients on the national transplant waiting list, including more than 90,000 patients awaiting kidney transplantation, and 20,000 patients waiting for life-saving heart, liver, and/or lung transplants. It is estimated that more than 28,000 solid organ transplant are performed in the USA on an annual basis.

   AST representatives should participate in the development of the risk based priority list which will guide the implementation of the proposed regulations on class III LDTs. Care should be taken that this process in not unduly influenced by commercial stakeholders.

   Locally developed and thoroughly validated alternatives are currently available for several FDA-approved kits, particularly kits that utilize nucleic acids based diagnostic methods for infectious disease. Furthermore, transplant recipients are susceptible to unusual and rare pathogens that are sometimes only detectable using in-house-developed assays. To avoid catastrophic disruption in medical care, it is essential that these in-house assays be allowed to continue within the respective institutions. There is no reason why hospital laboratories cannot implement local audits, personnel training, production/process/ document controls, corrective action mechanisms, and statistically driven quality assurance processes comparable to those provided by commercial vendors. It is understood that these in-house assays will use components that are legally marketed for clinical use, and will not be offered beyond local populations, or manufactured in high volume.

2. Class II, Moderate Risk, LDTs: The FDA envisages that moderate risk LDTs will be subject all regulations outlined above, but the implementation of these regulations will be phased in after oversight of Class III LDTs has been put in place. This process will also be guided by a priority list that will be announced within 4 years of

AST position: A complete listing of tests that fall in this category is not yet available. As a major stakeholder, AST should be included in advisory panels that will be set up to determine risk classifications. Tests already active on laboratory menus should be exempt from burdensome 510(k) premarketing submission requirements, particularly if their clinical validity is supported by existing scientific literature. It is important to note that these tests are performed in laboratories that are inspected by organizations such as College of American Pathologists (CAP), Occupational Safety and Health Administration (OSHA), and State Health Agencies. These laboratories are in compliance with the Clinical Laboratory Improvement Amendments Act (CLIA), and have intra-Department Quality Assurance Review programs, as well as internal mechanisms to report and investigate adverse events. Therefore, the FDA should carefully evaluate its plan to channel significant personnel and monetary resources into providing an additional layer of oversight to organizations that are already serving patients in an exemplary manner. A health care system that is already struggling to control costs should be spared these additional personnel and financial burdens.

It is worth noting that federal regulations for the implementation of CLIA already require 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. FDA has expressed a concern that CLIA fails to assess the safety and effectiveness of LDTs and does not evaluate clinical validity, but these requirements can be added to existing CLIA regulations without imposing a second layer of oversight over the entire laboratory operation. Likewise, provisions can be made for pre-market review and post- marketing safety monitoring for those LDTs that are going to be used to screen large populations outside of the local service area.

3. Class I, Low Risk, LDTs: According to the draft guidance, low risk LDTs will be subject to registration/listing and manufacture reporting requirements, but not to premarket review or quality system regulation.

   AST position: Laboratory tests that have been routinely, safely and effectively used for the past several decades be exempted from new registration and reporting requirements. So-called traditional LDTs include common clinical chemistries such as serum creatinine, blood glucose, liver function tests, and urine analysis, as well as routine histopathology and use of frozen sections, and immunohistochemical/in-situ hybridization techniques that use well characterized commercial reagents. Currently, tests in the latter category are commonly reported with a caveat that these tests are not FDA cleared, with an additional qualification that such clearance has been determined not be necessary by the FDA. AST does not believe that there is any reason to change the status quo for these low risk LDTs. These tests were developed to meet time sensitive needs that cannot be readily or economically met by the commercial sector.

AST thanks the Food and Drug Administration for the opportunity to provide this input to the draft guidance. Our members are available to provide any further information that may be helpful to the implementation of the proposed guidance. We do ask the FDA to be cognisant that this implementation will likely pose significant challenges to its current staffing and database capabilities.