



IDSAs

Infectious Diseases Society of America

2016-2017 BOARD OF DIRECTORS

President
William G. Powderly, MD, FIDSA
WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
ST. LOUIS, MO

President-Elect
Paul G. Auwaerter, MD, MBA, FIDSA
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE
BALTIMORE, MD

Vice President
Cynthia L. Sears, MD, FIDSA
JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE
BALTIMORE, MD

Secretary
Larry K. Pickering, MD, FIDSA
EMORY UNIVERSITY SCHOOL OF MEDICINE
ATLANTA, GA

Treasurer
Helen W. Boucher, MD, FIDSA
TUFTS MEDICAL CENTER
BOSTON, MA

Immediate Past President
Johan S. Bakken, MD, PhD, FIDSA
ST. LUKE'S ID ASSOCIATES
DULUTH, MN

Angela M. Caliendo, MD, PhD, FIDSA
BROWN UNIVERSITY/RHODE ISLAND HOSPITAL
PROVIDENCE, RI

Henry F. Chambers, MD, FIDSA
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
SAN FRANCISCO, CA

Janet A. Englund, MD, FIDSA
SEATTLE CHILDREN'S HOSPITAL
SEATTLE, WA

Thomas Fekete, MD, FIDSA
TEMPLE UNIVERSITY MEDICAL SCHOOL
PHILADELPHIA, PA

Joel E. Gallant, MD, MPH, FIDSA
SOUTHWEST CARE CENTER
SANTA FE, NM

Lawrence P. Martinelli, MD, FIDSA
COVENANT HEALTH
LUBBOCK, TX

Daniel P. McQuillen, MD, FIDSA
LAHEY HOSPITAL & MEDICAL CENTER
BURLINGTON, MA

Thomas A. Moore, MD, FIDSA
IDC OF KANSAS
WICHITA, KS

Trish M. Perl, MD, MSc, FIDSA
UT SOUTHWESTERN MEDICAL CENTER
DALLAS, TX

Chief Executive Officer
Christopher D. Busky, CAE

IDSAs Headquarters
1300 Wilson Boulevard
Suite 300
Arlington, VA 22209
TEL: (703) 299-0200
FAX: (703) 299-0204
EMAIL ADDRESS:
info@idsociety.org
WEBSITE:
www.idsociety.org

May 4, 2017

Jeffrey Shuren, MD, JD
Director
Center for Devices and Radiological Health
U.S. Food and Drug Administration
10903 New Hampshire Avenue
W066-5431
Silver Spring, MD 20903

Dear Dr. Shuren,

The Infectious Diseases Society of America (IDSAs) recognizes that the Food and Drug Administration (FDA) is committed to protecting patients. Our society has closely followed the FDA's draft guidance, public stakeholder workshop, and January 2017 discussion paper proposing to regulate laboratory developed tests (LDTs). In April 2016, IDSAs published an [article](#) in *Clinical Infectious Diseases* (CID) which outlined the limitations the FDA draft guidance would place on patient access to ID testing and provided recommendations designed to help minimize the disruption of LDTs in the care of patients suffering from infection. We appreciate that the recent discussion paper aims to take into consideration many of the comments FDA received on the draft guidance, but remain concerned that many of the ideas set forth in the discussion paper would still negatively impact the care of patients being evaluated for infectious diseases (ID) if implemented.

IDSAs agrees that increased regulation of LDTs is needed to ensure safety and effectiveness in some select cases, but for the vast majority of ID LDTs there is no data to support the assertion that these cause harm. Many LDTs are already validated and performed under a system of regulations by the College of American Pathologists (CAP) and the Clinical Laboratory Improvement Amendments (CLIA), which provide adequate protections in most instances. IDSAs would like to work with FDA to identify the appropriate regulatory balance to ensure that patients have access to high quality testing and to promote diagnostic innovation.

FDA's discussion paper focuses on new and significantly modified high- and moderate-risk products and would exempt "grandfathered" products from most FDA regulatory controls, which IDSAs appreciates; however, as tests are improved or modified they will ultimately fall under regulatory jurisdiction, and most not-for-profit clinical laboratories do not have the resources necessary to navigate the premarket review process. This would severely curtail the ability of laboratories to develop and utilize novel LDTs designed to address unmet medical needs, thereby seriously limiting patient access to tests and innovation (including developing new LDTs for emerging threats).

IDSA is also grateful for FDA’s proposal to grandfather LDTs used solely for public health surveillance, which are not used to guide treatment. However, we recommend developing a system for expedited review or enforcement discretion for the use of LDTs in outbreaks of public health significance. It is important that the emergency use authorizations (EUA) process be streamlined and clear about the testing requirements to move LDTs through the process in a more expeditious and transparent manner; this will ease the burden on public health laboratories while still maintaining quality and accurate testing standards.

Limitations and concerns

While LDTs for rare diseases are included as a category of grandfathered LDT in the discussion paper, the term “rare disease” is not clearly defined. In its draft guidance for LDTs, FDA recommended defining rare diseases as those that are tested for no more than 4000 times each year nationwide. However, 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 those rare infections to be either diagnosed or ruled out, they must be tested for at far higher rates than the FDA limit of 4000/year nationwide. The FDA Center for Drug Evaluation and Research (CDER) defines rare diseases as those that affect fewer than 200,000 patients nationwide, based on the 1983 Orphan Drug Act. 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.

The importance of the speed of testing and results is unique to ID among disease areas; losing access to LDTs could mean that more hospitals need to send tests to reference labs, which may delay the results from hours to days and severely impact patient care. In 2014, FDA issued a pair of guidance documents on this issue entitled “Expedited Access for Premarket Approval of Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions” and “Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval.” IDSA applauded these guidances for taking steps to speed patient access to urgently needed diagnostic tests, and we recommend that FDA extend this level of flexibility to LDTs that it intends to regulate.

Unlike other disease areas, the evidence that ID LDTs provide unreliable results that lead to harmful patient care decisions is lacking. Given the important role of diagnostics in ID patient care, IDSA is concerned about the prioritization and classification of LDT risks and the prospective impediment to rapid response to ID emergencies under the FDA’s current risk stratification proposal. For instance, the Class II device characterization contains a multitude of tests for numerous analytes such that the required pre-market review will severely limit the ability of labs to provide necessary LDTs to fill particular diagnostic niches. LDTs serve a significant, often vital, purpose in infectious disease diagnostics: 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.

Opportunities for collaboration

IDSA recognizes that FDA regulation of the highest-risk tests may be warranted, but recommends a more granular prioritization and classification of risk that takes patient needs

and laboratory capacities into account. We urge FDA to 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 FDA's review panels to classify LDT risk.

The FDA discussion paper endorses a focus on analytical and clinical validity as the basis for test approval. IDSA agrees that independent premarket review of a test's validity is becoming increasingly important to providing high-quality health care, and we would be pleased to help convene experts to poll literature and other sources of information such as clinical practice guidelines to identify tests that have appropriate information that establishes their safety and clinical validity. In May 2016 IDSA provided FDA with a [literature review of tests for transplant associated viruses](#) to assist with classification determinations, and we were pleased that FDA convened an expert panel meeting last fall devoted to viral load testing for transplant-associated opportunistic viral infections. It is our hope that a similar mechanism for LDT classification would limit the need of laboratories to undertake duplicative efforts to demonstrate clinical utility that has already been proven. In addition, expert panels that include clinical microbiologists and ID physicians could be convened to help establish standardized guidance and requirements for the determination of analytical validity.

Infectious diseases LDTs exemplify bench to bedside innovation that allows patients and physicians access to cutting-edge quality enhancements in patient care. Hopefully, FDA oversight activities will facilitate the ever-changing needs of timely test development. IDSA understands that the FDA discussion paper, which synthesizes stakeholder feedback and outlines a prospective approach to regulation, does not represent the formal position of the FDA, nor does it constitute an enforceable standard or final version of the draft guidance. IDSA is well-positioned to collaborate with federal agencies, Congress, and external professional societies to develop a balanced and empirical approach to LDT regulation that does not inhibit management of complex critically ill patients or response to emerging threats, and looks forward to continuing to work with FDA and associated stakeholders on this evolving issue.

Sincerely,

A handwritten signature in black ink that reads "Bill Powderly". The signature is written in a cursive, slightly slanted style.

William G. Powderly, MD, FIDSA
President, IDSA