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# IDSAs

Infectious Diseases Society of America

April 27, 2018

Scott Gottlieb, MD

Commissioner

U.S. Food and Drug Administration

10903 New Hampshire Avenue

Building 1, Room 2217

Silver Spring, MD 20993

Dear Commissioner Gottlieb:

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 FDA, industry, and legislative proposals to regulate laboratory developed tests (LDTs). We are pleased to offer comments on the draft Diagnostic Accuracy and Innovation Act (DAIA) that builds upon previous efforts to establish a modern framework for the regulation of LDTs, as FDA offers technical assistance on the discussion draft to Congress. We appreciate the opportunity to discuss the important role of infectious disease (ID) LDTs in clinical care and public health and the impacts of the proposed legislation on innovation and patient access to testing. IDSAs looks forward to working with FDA and Congress to craft appropriate policies to spur advancement and protect patient access to high-quality diagnostic testing.

## Background

Our society has stressed the importance of innovative diagnostic devices that support the care of patients suffering from infectious diseases, most notably in the 2015 IDSAs report, [Better Tests, Better Care: The Promise of Next Generation Diagnostics](#). Diagnostics help determine appropriate treatment, increasing the likelihood of a positive patient outcome while decreasing the overuse or misuse of antibiotics that significantly contribute to the development of antimicrobial resistance. ID LDTs are often developed to test for pathogens for which there are no commercial tests available on the market. LDTs frequently represent the most rapid testing option available at many institutions, especially if the only alternative is sending specimens to an external reference laboratory for testing. In infectious diseases, such delays of even a few hours can have a devastating impact on patients and subsequently affect public health. Notably, high-quality ID diagnostics have a unique ability to protect public health as a critical component of protocols to contain outbreaks and prevent the transmission of infectious agents. With new ID threats frequently emerging, it is important to maintain patient access to high-quality testing and promote innovation.

ID LDTs have been used to diagnose and manage a variety of infectious diseases for over two decades. ID physicians and clinical microbiologists have acquired a great deal of experience with these tests. ID LDTs are almost always well designed and validated for reliable use in patient care. In many instances, they have become the diagnostic standard of care, often significantly preceding the availability of FDA-approved tests for the same analyte (e.g., CMV viral load monitoring in cardiac transplant patients). We recognize that there are valid concerns about the risks associated with LDTs, particularly in areas such as oncology or genetic testing. However, these risks are not equal across all areas of medicine. 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. We believe the potential risks of ID LDTs are minimal compared to their advances and benefits to patient care.

Given the important role of diagnostics in ID patient care, IDSA has been highly engaged in the ongoing policy discussions regarding LDT regulation. Our Society has provided [comments](#) on the 2014 FDA draft guidance, [responded](#) to a 2015 House Energy and Commerce Committee discussion draft, published a [joint position paper on LDTs](#), offered a [statement](#) following the 2016 Senate Health, Education, Labor and Pensions Committee hearing on LDTs, [responded](#) to the FDA January 2017 discussion paper, and [commented](#) on the DAIA discussion draft. We strongly believe that any new policies regarding the oversight of laboratory test approval should maintain patient access to high-quality testing options and promote innovation.

IDSA welcomes this discussion draft and acknowledges that it makes several key improvements upon previously proposed regulatory frameworks. However, we are very concerned about the classification of all LDTs (referred to in the discussion draft as “laboratory test protocols”) within the proposed new regulatory category of in vitro clinical tests (IVCTs), which includes modified FDA jurisdiction over “the design, development, and validation of an IVCT as well as the production of an IVCT for distribution to another facility or third-party.” Furthermore, we remain concerned that the discussion draft may still lead to many problems, some of which we previously identified with the FDA draft guidance and the 2015 Energy and Commerce Committee discussion drafts. To this end, we would like to request clarification as to whether FDA oversight will apply only to those laboratories that design, develop, validate **and** distribute an IVCT outside of their facility, institution, or regional network (e.g., a test that is manufactured and sold/distributed to other laboratories) or whether FDA oversight would also apply to those tests that are utilized by a laboratory only for their respective patient population and that of other facilities in the region for whom the laboratory serves as a regional reference laboratory.

**We would like to offer specific questions, concerns, and recommendations on the new discussion draft below as well as express support for certain provisions. We hope our recommendations will be useful in your endeavors and we would greatly appreciate the opportunity for continued dialogue on this important issue.**

#### **Public health surveillance exemption**

IDSA is pleased to see that the DAIA discussion draft includes a provision to exempt public health surveillance activities from the proposed regulations. We strongly agree that surveillance

is essential to maintaining public health response and we support excluding tests from FDA oversight. **We believe this exemption should apply only to tests used by public health laboratories and have urged the bill sponsors to make this clear in future drafts of this legislation.**

### **Single approach for commercial test developers and clinical laboratories**

IDSA appreciates that the DAIA discussion draft expands on previous descriptions of the proposed premarket review process. As stated in our prior comments on the Energy and Commerce Committee 2015 discussion drafts, we strongly oppose regulating large-scale commercial entities in the same manner as clinical and other not-for-profit laboratories in how they design, validate, and use diagnostic tests. We remain extremely concerned that the draft does not adequately address the issue, as clinical and not-for-profit laboratories lack the resources to navigate the premarket review process and meet the proposed post-market obligations to generate evidence demonstrating assurance of clinical validity. The application of the same regulatory principles regardless of where the test is developed does not consider the disparity in resources between these settings. While it is customary that for-profit entities like commercial manufacturers have dedicated regulatory affairs departments, clinical laboratories typically lack such departments or the financial resources to develop such departments *de novo*. This would put clinical laboratories at a clear and distinct disadvantage in their ability to develop new LDTs and provide expert support to physicians regarding their use, in turn curtailing innovation and patient access to testing. The potential outcome would be an inability to provide rapid, accurate diagnoses for patients. This will foster, for example, inappropriate use of antibiotics and mistreatment of an undiagnosed infection.

It is inappropriate, in our view, to hold tests developed and used by non-commercial clinical laboratories to the same requirements as tests developed and marketed commercially, given the very different ways in which the tests are developed and used. For example, a large manufacturer may develop a commercial test that will be used in widely dispersed geographic areas, where local factors can drive variability in test performance. The complex validation requirements necessary for such a commercial test scenario (e.g., clinical trials) typically would not apply to clinical laboratories that use their ID LDTs only for their local hospital system or related community hospitals. Thus, we remain concerned that DAIA would still severely impede the ability of clinical laboratories to develop and utilize ID LDTs for the patient's needs, in turn severely limiting innovation of novel ID LDTs for rapidly emerging infectious diseases.

**IDSA recommends the application of oversight discretion for tests that are developed and used to treat patients within one facility, a network of related facilities (such as a hospital system), public health laboratories, and possibly for reference laboratories that provide testing for both local hospitals and local physician practices.** Under such a scenario, analytic validation would still be required for these tests and could continue to be regulated by the Centers for Medicare & Medicaid Services (CMS) under 42 CFR 493.1253.

### **Low-risk designation for all platforms**

The DAIA discussion draft proposes to consider all platforms, “including software used to effectuate the hardware’s functionality,” as low risk. We remain concerned that the definition of the software is unclear. For example, data sets for sequencing are used to identify human

immunodeficiency virus (HIV) drug resistance and Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) systems for bacterial, mycobacterial, and fungal identification. It is unclear if the legislation would include such databases in the definition of software. These database sets can have a significant impact on patient care, and we do not consider them low risk. **Therefore, we request clarifying language to include certain types of software within the definition of a platform. Given that the platform definition would now include software databases like the above examples, we also recommend removing language that would automatically designate platforms as low risk. The oversight process should ensure their risks are assessed appropriately.**

### **Classification and reclassification processes**

In general, we believe the discussion draft's risk-based classification schematic is reasonable and we applaud its iterative approach of allowing developers or FDA to redefine risk as more becomes understood about the test. Also, we strongly support the repeated call for advisory panels to provide recommendations to the Secretary on risk classification of both new and existing tests as well as opportunities for public comment. The expertise of clinicians and laboratory professionals who understand the use of tests and their impact on patient care will be critical in ensuring that tests will be classified appropriately. We strongly urge FDA to consider the inclusion of both doctoral level clinical microbiologists and ID physicians on advisory panels dealing with ID diagnostics, including ID LDTs.

IDSA also recognizes the appropriateness of considering “risk reducing factors” (page 15, line 22—page 16, lines 1-10) in test classification, including whether the test's technology and clinical use are well characterized as well as the availability of other tests (such as confirmatory or adjunctive tests) or relevant materials standards. However, we believe more specific guidelines on what levels of characterization would help determine high, moderate, or low risk would be very helpful. Some tests, even if they are well characterized, may still represent a high risk that cannot be adequately mitigated. Further, other tests for serious or life-threatening infectious diseases may only carry moderate risk, which was allowed under previous discussion drafts' definitions of risk.

We also encourage FDA to consider the risks posed by classifying transplant-associated LDTs, which have years of supporting analytical data, as high risk, or Class III tests. A Class III designation requires developers to submit a premarket approval (PMA) application for any new commercial test. The associated costs often deter much-needed innovation that would lead to improvements in clinical care. IDSA is concerned that this area of testing may become seriously compromised under DAIA, and we urge FDA to classify tests for transplant-associated viruses as Class II.

### **Special Pathways for Certain Tests**

IDSA appreciates that the DAIA discussion draft includes special pathways for certain categories of tests, including tests for unmet medical needs and those for rare diseases. Requiring reasonable assurance of clinical validity for intended use with a three-year postmarket obligation provides FDA and commercial test developers more flexibility in establishing a balanced plan that satisfies clinical validity for a test while ensuring patient access to innovative testing.

DAIA defines rare diseases as those with an incidence of 8,000 patients a year nationwide, or prevalence of 50,000 patients total. The FDA Center for Drug Evaluation and Research (CDER) defines rare diseases, based on the 1983 Orphan Drug Act, as those that affect fewer than 200,000 patients nationwide. We are concerned that the discussion draft deviates from the Orphan Drug Act definition of 200,000 patients nationwide which may potentially restrict tests for certain rare diseases higher in incidence or prevalence. We, therefore, propose that the regulation of rare disease laboratory test protocols aligns with this definition to permit continued enforcement discretion for LDTs for diseases with fewer than 200,000 patients in the United States.

The discussion draft's regulatory pathway premarket requirements are appropriate, given the difficulty for developers to establish the clinical validity of a test for a rare disease. However, we are concerned that clinical laboratories would find it exceedingly challenging to perform the postmarket data collection needed to establish clinical validity through this pathway, given the lack of available resources to do so. As these same laboratories are the most likely developers of such tests for rare diseases, we believe this pathway's design will hamper, rather than improve, patient access to tests for rare diseases.

#### **Custom IVCTs**

As written, the DAIA discussion draft provides for development of custom IVCTs that appear to be exempt from the regulatory requirements of other LDTs (e.g., premarket review, etc.) provided that the test is “developed in order to comply with the order of an individual physician, dentist or other healthcare professional” in the event that no other IVCT is available. As currently worded, such testing would be developed on a case-by-case basis. We are very concerned about this approach, which appears to violate the expected and accepted practices for laboratory testing as regulated under 42 CFR 493.1253 by foregoing the establishment of analytical validity. Critically, the performance of testing that caters exclusively to an individual physician request without regard to the appropriateness of the test requested is contrary to the practice of laboratory medicine.

#### **Exception for emergency use**

IDSA was disappointed to see that unlike the May 2015 Energy & Commerce Committee discussion draft, the DAIA discussion draft does not explicitly provide a special category for the rapid development and approval of tests during public health emergencies. While we had concerns about the exemption as designed in the 2015 draft, we applauded the Committee's decision to include a pathway to ensure appropriate public health responses to outbreaks. **We recommend the exemption for tests developed in response to public health emergencies be reconsidered for inclusion in the bill. Given the key role public health laboratories play in outbreaks, we again recommend that any tests developed or used by public health laboratories for emergency use purposes be exempted from the new oversight proposed in the discussion draft.**

#### **Sec. 4: FDA fees (page 156, line 10—page 160, line 25)**

Our society appreciates that the DAIA discussion draft requests the input of scientific and academic experts, health care professionals, and patient advocacy groups to determine the initial recommendations for IVCT application review, followed by a public comment period to review

proposed user fee recommendations. However, the suggestion to limit user fees to 30% of the costs of reviewing IVCT applications, combined with the removal of the 2015 discussion draft's credit against FDA user fees for additional regulatory fees paid, would be detrimental to the development of ID LDTs. While a fee limited to 30% of the costs of reviewing IVCT applications costs is mentioned, the full cost used to make such calculations is thus far unknown. It is unclear whether not-for-profit laboratories would be required to pay these fees and whether this fee would apply to all IVCTs, or only to those that will be sold/distributed by the "developer." We recommend that any fees and fee structuring should be made clear in any proposed legislation.

Furthermore, IDSA strongly recommends that an economic impact analysis of high- and moderate-risk applications be performed as this legislation is being considered. This analysis should also take into account the cost of experiments to demonstrate analytical and clinical performance as well as an estimate of pre-submission and postmarket institutional review costs. This will be a critical component to assessing the financial feasibility for clinical laboratories to comply with the proposed regulation. We remain deeply concerned that if clinical microbiology laboratories are required to pay user fees during submission of new tests, this will add another severe burden that will hinder the development of new LDTs and thus patient access to testing. Moreover, these higher costs of testing would likely be passed on to patients, increasing healthcare costs.

**IDSA therefore strongly urges any LDT legislation to consider exempting clinical microbiology laboratories and public health laboratories from any FDA user fees.**

### **Section 5. Certification of Laboratories (CLIA)**

The Clinical Laboratory Improvement Amendments of 1988 are the central foundation that governs all aspects of testing in clinical laboratories. As stated in the section-by-section overview of the DAIA discussion draft, CLIA standards will be enhanced for laboratory computer systems, including standards for security, data integrity, autoverification, and internal controls of software modifications. While we are supportive of the overall goal of modernizing the CLIA program at CMS to maintain quality laboratory operations, as written, there is no information regarding how this will proceed. IDSA recommends that additional information be provided regarding what components will be contained within the planned modernization program.

We would also appreciate clarification of what constitutes the practice of medicine under portion (B) of this section. As proposed, the authority to regulate the practice of medicine under this section is reserved for the individual states. To our knowledge, this language is not present in CLIA currently. We would appreciate additional information regarding the thinking for including this language at this time. Finally, we strongly believe that increased regulatory review is unlikely to advance innovation. The process should be balanced to ensure proper validation/verification of diagnostic tests, but in a way that utilizes existing mechanisms (e.g., CLIA, CAP, New York State requirements) for demonstrating performance accuracy of non-commercialized laboratory-developed tests.

### **Options for Rapid Testing Are Essential**

IDSA strongly cautions the federal government against adopting policies that will severely limit the ability of clinical laboratories in academic medical centers to develop and use LDTs. While we appreciate the inclusion of a grandfather clause that minimizes disruption to tests currently in use (such as exempting IVCTs introduced by laboratories prior to three months before enactment of the bill from regulatory requirements for five years), we are concerned that new test development needed to keep pace with rapidly changing ID threats will be hindered, particularly at major medical centers that specialize in the management of complex, critically ill patients. These centers regularly develop LDTs to provide the highest level of care as new diseases emerge and new therapies are needed. Despite the new regulatory standards proposed in the discussion draft (such as the removal of 501(k) premarket submission requirements), these same laboratories still lack the financial and administrative resources for even one moderate risk test premarket submission, let alone submissions for all new LDTs. It is highly unlikely these laboratories would be able to navigate the high-risk test premarket submission process or the postmarket obligations.

Under such a scenario, these laboratories will likely move to predominant, or exclusive, use of commercial diagnostic tests or send samples for testing to outside reference laboratories, both of which can pose 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. Such investment will not be feasible for many hospital laboratories or, if made, may result in increased costs to the patient.

Alternatively, sending clinical specimens to reference laboratories for testing would significantly increase the turnaround time required to get the results to physicians (for those few that could handle the sudden increase in volume). Rapid diagnostics that facilitate early initiation of life-saving treatment are critical in ID patient care, where even a few hours' delay can negatively impact patient outcomes. Public health responses also require rapid identification of an emerging health risk, and any delay in activation of important public health protocols allows dangerous infections to spread. Stays incurred by sending specimens to reference laboratories with requirements for transport time and inflexible testing schedules may significantly impede detection of ID outbreaks. Lastly, commercial laboratories may lag considerably in making new tests available as new diseases emerge, hampering our full understanding of what constitutes test accuracy for an emerging infection and putting patient safety and public health at risk. The consequence would be a delay in available testing and results and an anti-development environment that is anti-competitive from the perspective of test development and test pricing.

### **Opportunities for collaboration**

IDSA agrees that independent premarket review of test validity is becoming increasingly important to providing high-quality health care. We would be pleased to help convene experts for literature review and assessing 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 the FDA subsequently convened an expert panel meeting last fall devoted to viral load testing for transplant-associated opportunistic viral infections. We hope that a similar mechanism for LDT classification would limit the need for laboratories to undertake duplicative efforts to demonstrate clinical utility that has already been proven. Additionally, 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.

ID LDTs exemplify bench to bedside innovation that allows patients and physicians access to cutting-edge quality enhancements in patient care. We remain concerned that many of the ideas outlined in the DAIA discussion draft would negatively impact patients evaluated for infectious diseases. IDSA is available and well-positioned to collaborate with federal agencies, Congress, and additional 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. We appreciate your close attention to these important and complex issues, and look forward to working together to craft appropriate policies to spur innovation and protect patient access to high-quality diagnostic testing.

Sincerely,

A handwritten signature in black ink, appearing to read "Paul G. Auwaerter". The signature is fluid and cursive, with a long horizontal stroke extending to the right.

Paul G. Auwaerter, MD, MBA, FIDSA  
President, IDSA

**Cc: Jeffrey Shuren, MD, JD, Director, FDA Center for Devices and Radiological Health**