



AMERICAN  
SOCIETY FOR  
MICROBIOLOGY



IDSA  
Infectious Diseases Society of America



April 7, 2017

The Honorable Larry Bucshon, MD  
1005 Longworth House Office Building  
Washington, DC 20515

The Honorable Diana Degette  
2111 Rayburn House Office Building  
Washington, DC 20515

Dear Representatives Bucshon and DeGette,

The Infectious Diseases Society of America (IDSA), the Pan American Society for Clinical Virology (PASCV), and the American Society for Microbiology (ASM) are pleased to offer comments on the draft Diagnostic Accuracy and Innovation Act (DAIA), which builds upon previous efforts to establish a modern framework for the regulation of both *in vitro* diagnostic tests and laboratory-developed tests (LDTs). We appreciate the opportunity to share our perspective about the important role of infectious disease (ID) LDTs in clinical care and public health, and the potential impact the proposed regulations may have on innovation and patient access to testing. We appreciate your close attention to these important and complex issues, and look forward to working with you to craft appropriate policies to spur innovation and protect patient access to high quality diagnostic testing.

**Background:**

Over the past several years, our societies have stressed the importance of innovative diagnostic devices that support the care of patients suffering from infectious diseases, most notably in the 2015 IDSA report, [Better Tests, Better Care: The Promise of Next Generation Diagnostics](#). ID physicians and non-ID physicians alike rely upon diagnostics, both LDTs and commercial tests, to identify the pathogen(s) infecting a patient and determine associated antimicrobial susceptibility. Diagnostics determine appropriate treatment, increasing the likelihood of a positive patient outcome and 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 other alternative is sending specimens to an external reference laboratory for testing. In infectious diseases, such delays in testing 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 the broader 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, and 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). IDSA, PACSV and ASM 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, and there is little evidence that clinical ID LDTs provide unreliable results that lead to harmful patient care decisions. 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, PACSV, and ASM have been highly engaged in the ongoing policy discussions regarding LDT regulation, providing [comments on the 2014 Food and Drug Administration \(FDA\) draft guidance](#), [responding to a 2015 House Energy and Commerce Committee discussion draft](#), publishing a [joint position paper](#) on LDTs, offering a [statement](#) following the 2016 Senate Health, Education, Labor and Pensions Committee hearing on LDTs, and responding to FDA's January 2017 discussion paper. 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.

We welcome this discussion draft and acknowledge 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 FDA's 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 several 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 with you on this important issue.**

### **Sec. 3. Regulation of *In Vitro* Clinical Tests**

#### **Public Health Surveillance Exemption**

IDSA, PACSV, and ASM are pleased to see that this 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 responses, and we support excluding tests with these uses from FDA oversight. **We believe this exemption should apply only to tests used by public health laboratories, and urge you to make this clear in future drafts of this legislation.**

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

IDSA, PASCV, and ASM appreciate that the DAIA discussion draft expands on previous descriptions of the proposed premarket review process. As stated in our prior comments on the Committee’s 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 issues that we previously raised with the earlier Energy and Commerce Committee discussion drafts and draft regulatory framework, namely that clinical and not-for-profit laboratories do not have the resources necessary to navigate the premarket review process or to meet the proposed postmarket 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 take into account 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 provide for physicians using LDTs, in turn curtailing patient access to testing.

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 own ID LDTs only for their local hospital system or related community hospitals, and would place an undue burden on their ability to develop new, innovative tests. Thus, we remain concerned that the DAIA would still severely impede the ability of clinical laboratories to develop and utilize ID LDTs, in turn seriously limiting patient access to innovative tests needed to guide optimal treatment. This would severely limit innovation of novel ID LDTs for rapidly emerging infectious diseases.

**IDSA, PASCV and ASM recommend 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 (page 21, lines 11-18)**

The discussion draft proposes to consider all platforms, defined as both the instrument and the software needed to run a test, as low risk. We remain concerned that the definition of the software needed to run a test 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. **We therefore request that information regarding what types of software are considered part of a testing platform be more clearly defined. Should this definition include software databases like the above examples, we recommend that the discussion draft call for the implementation of an oversight process to ensure their risks can be assessed appropriately.**

#### **Classification and reclassification processes**

In general, we believe the discussion draft's risk-based classification is reasonable and applaud its iterative aspect that would allow developers or FDA to redefine risk as more becomes understood about the test. In addition, we strongly support the discussion draft's repeated call for the use of 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, PASCV and ASM also recognize the appropriateness of considering "risk reducing factors" (page 15, line 22—page 16, lines 1-10) in a test's 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.

#### **Premarket Review**

We greatly appreciate your efforts to streamline the regulatory process for premarket submission of high and moderate risk tests, which we believe will allow more rapid patient access to innovative new ID diagnostics developed by commercial manufacturers. The discussion draft requires that "reasonable assurance" (page 37, lines 4-8) of both clinical and analytical validity (defined on page 7, line 12—page 8, line 14) be determined. IDSA, PASCV, and ASM also appreciate that the discussion draft includes explicit definitions of clinical and analytical validity, and that the draft includes language to define what may constitute the "valid scientific evidence" that must be presented in a test's premarket approval application (page 12, lines 1-15).

#### **Premarket Requirements for Modifications (page 88, line 10—page 93, line 8)**

IDSA, PASCV and ASM applaud the discussion draft's approach to exempt certain activities, such as using a different analyte for a commercial test, from triggering FDA premarket oversight as long as the intended use remains unchanged and no new meaningful clinical impact occurs. We would recommend inclusion of a clear definition of the term "meaningful clinical impact". Often, improvement in instrumentation occurs during the lifespan of a given set of reagents. These can lead to improved analytical performance characteristics (enhanced sensitivity and

specificity) that lead to altered but improved clinical performance. A least burdensome process for updating high- and moderate-risk IVCTs should be devised to encourage evolution of tests with better performance.

IDSA, PASCV, and ASM are particularly pleased that the second discussion draft includes new language to specify that a premarket application shall not be required with respect to a modification of a moderate or high risk test if the modification is specimen-related so long as the specimen would not alter the intended use of the test. This would allow, for example, the use of a test designed for detecting cervical *Neisseria gonorrhoeae* to be used on rectal swabs. However, we would appreciate additional granularity regarding the definition of “intended use”. The 2015 Centers for Disease Control and Prevention (CDC) sexually transmitted disease (STD) guidelines state that rectal and pharyngeal screening for *N. gonorrhoeae* must be performed by nucleic acid amplification testing (NAAT). Urogenital specimens are the only approved sources for the currently available FDA-cleared NAAT *in vitro* diagnostics, forcing clinical laboratories to modify these tests for rectal or throat specimens. The discussion draft indicates that a commercial test used on a specimen other than what was originally approved would be considered subject to oversight. As stated above, clinical laboratories would be unable to complete a premarket submission application for this new test, and would likely cease testing, thereby limiting patient access to these critical LDTs.

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

IDSA, PASCV, and ASM appreciate 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.

### **Custom IVCT’s**

As written, the DAIA discussion draft provides a pathway for development of custom IVCTs that appear to be exempt from the regulatory requirements of other LDT’s (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 health care professional” in the event that no other IVCT is available. As written, such testing would be developed on a case-by-case basis. We are very concerned about this approach, which appears to also violate the expected and accepted practices for laboratory testing as regulated under 42 CFR 493.1253 by appearing to forgo the establishment of analytical validity. Critically, the performance of testing that caters exclusively to an individual physician’s request without regard to the appropriateness of the test requested is contrary to the practice of laboratory medicine.

### **Exception for rare diseases and conditions (page 10, lines 5-16, page 49, lines 17-23)**

The DAIA discussion draft defines rare diseases as those with an incidence of 8,000 patients a year nationwide, or a 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’s deviation from the Orphan Drug Act’s definition of 200,000 patients nationwide may potentially

restrict tests for certain rare diseases that are larger 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. Given that 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.

**As stated previously, IDSA, PASCV, and ASM recommend that all tests developed by clinical laboratories for use within one facility, a network of related facilities (such as a hospital system), and possibly for reference laboratories that provide testing for local hospitals and local physician practices be exempt from additional oversight by FDA. If oversight discretion in these instances is not feasible, we recommend that at least all tests to diagnose rare diseases developed by clinical laboratories for the uses described above be exempted from the oversight framework proposed in the discussion draft.** Under such a scenario, analytic validation would still be required for these tests and could continue to be regulated by CMS under 42 CFR 493.1253.

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

IDSA, PASCV and ASM are 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 with 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 and/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)**

IDSA, PASCV, and ASM appreciate 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. We urge FDA to ensure that both doctoral-level clinical microbiologists and ID physicians are included in this input process. However, the suggestion to limit user fees to 30 percent 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. Please clarify 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, PASCV, and ASM strongly recommend 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.

IDSA, PASCV, and ASM 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 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, PASCV, and ASM therefore strongly urge that you 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 (CLIA) 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 security standards, data integrity, autoverification standards, and standards for 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 on what will be modernized or how. IDSA, PASCV, and ASM recommend that additional information be provided regarding what components will be contained within the planned modernization program.

IDSA, PACSV, and ASM are deeply concerned about the potential for duplicative regulation introduced by the proposed CLIA additions. A significant portion of the addition to CLIA focuses on quality systems. However, following quality indicators over time is part of good laboratory practice that is performed routinely as part of adherence to CLIA currently and requirements for laboratory accreditation by entities such as the College of American Pathologists (CAP) that enforce CLIA through deemed status. Furthermore, laboratories that are inspected by CAP and/or the Joint Commission must adhere to quality indicators that mandate tracking test performance. However, reporting to federal authorities by individual laboratories is currently not performed but would be mandated under the proposed changes. Clinical laboratories spend significant time, energy and money preparing for inspections by accrediting agencies. We are concerned about the potential additional burden placed on clinical laboratories should they perform LDT testing and require inspection by FDA. We therefore recommend that any proposed changes to CLIA are reevaluated to avoid the creation of duplicative regulation.

We would also appreciate further 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 to 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) of demonstrating accurate performance of non-commercialized laboratory developed tests.

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

IDSA, PASCV and ASM strongly caution the federal government against adopting policies that will severely limit the ability of clinical laboratories in academic medical centers from developing and using LDTs. While we appreciate the proposal's 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 the new test development that is 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, but despite the new regulatory standards proposed in the discussion draft (such as the removal of 501(k) premarket submission requirements), these same laboratories will 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. Delays 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.

In summary, both ID LDTs and commercial tests play important roles in the care of patients with infectious diseases, and we reiterate that economic incentives and appropriate regulation for both types of diagnostics are needed to ensure patients, and their physicians, have access to cutting edge quality enhancements in patient care. IDSA, PACSV, and ASM also offer the expertise of its members to assist in continuing efforts to improve the regulatory environment for diagnostics. Once again, we greatly appreciate Congress's ongoing commitment to patient care and public health and your willingness to engage on this complex issue. We look forward to continuing to provide our perspective and expertise to stakeholders and working with you to craft appropriate policies to spur innovation and protect patient access to high quality diagnostic testing. Should you have any questions, please do not hesitate to contact Jaclyn Levy, IDSA's Senior Program Officer for Science & Research Policy, at [jlevy@idsociety.org](mailto:jlevy@idsociety.org) or 703-299-1216.

Sincerely,

Handwritten signature of William G. Powderly in black ink.

William G. Powderly, MD, FIDSA  
President, IDSA

Handwritten signature of Susan E. Sharp in black ink.

Susan Sharp, Ph.D., D(ABMM), FAAM  
President, ASM

Handwritten signature of Alexandra Valsamakis in black ink, enclosed in a thin black rectangular box.

Alexandra Valsamakis, MD, Ph.D.  
President, PASCV

ASM is the world's largest scientific Society, comprised of approximately 50,000 professionals in the microbiological sciences. ASM members work in educational, research, industrial, and government settings on issues such as the environment, the prevention and treatment of infectious diseases, laboratory and diagnostic medicine, and food and water safety. Many of ASM's members have primary involvement in clinical laboratory medicine including individuals directing clinical microbiology, immunology and molecular diagnostic laboratories.

IDSA represents over 10,000 infectious diseases physicians and scientists devoted to patient care, disease prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections, including meningitis, pneumonia, tuberculosis, HIV/AIDS, antibiotic-resistant bacterial infections such as those caused by methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin-resistant enterococci (VRE), and Gram-negative bacterial infections such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and, finally, emerging infectious syndromes such as Ebola virus fever, enterovirus D68 infection, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and infections caused by bacteria containing the New Delhi metallo-beta-lactamase (NDM) enzyme that makes them resistant to a broad range of antibacterial drugs.

The PASCV is an international society whose members perform laboratory testing for the detection, quantification, and characterization of viral pathogens. PASCV membership includes physicians, doctoral-level scientists, and medical technologists, representing academic medicine, clinical laboratories, commercial laboratories, the pharmaceutical industry, and in vitro diagnostics manufacturing.