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IDSA
Infectious Diseases Society of America

June 19, 2015

The Honorable Fred Upton, Jr.
Chairman, Energy & Commerce Committee
2183 Rayburn House Office Building
Washington, DC 20515

The Honorable Frank Pallone, Chairman,
Ranking Member Energy & Commerce Committee
237 Cannon House Office Building
Washington, DC 20515

Dear Chairman Upton and Representative Pallone,

The Infectious Diseases Society of America (IDSA) is pleased to offer comments on the discussion draft to establish a regulatory framework for both *in vitro* diagnostic tests and laboratory developed tests (LDTs). We appreciate the Committee's close attention to this important issue, which has significant implications for patient care and public health.

Over the past several years, IDSA has stressed the importance of innovative diagnostic tests for the care of patients suffering from infectious diseases (ID), most notably in our recent report, Better Tests, Better Care: The Promise of Next Generation Diagnostics. Improved diagnostics, both commercial tests and LDTs, can allow physicians to rapidly identify the pathogen infecting a patient and prescribe the most appropriate treatment, increasing the likelihood of a positive patient outcome. Notably, high quality ID diagnostics have a unique ability to protect the broader public health by alerting health officials of the need to trigger protocols to contain outbreaks and prevent the transmission of infections and by guiding clinicians regarding the appropriate use of antimicrobial drugs that is critical for limiting the development of resistance.

IDSA recognizes that there are valid concerns about the risks associated with LDTs in areas such as cancer and genetic testing, as well as infectious diseases. While many ID LDTs have a long history of safe and effective use in patient care, other ID LDTs may not have been evaluated as rigorously. Nonetheless, IDSA believes the risks raised by the use of ID LDTs are dwarfed by their advances and benefits to patient care. Unlike other disease areas, significant evidence that most ID LDTs provide unreliable results that lead to harmful patient care decisions is lacking.

IDSA appreciates the spirit of the discussion draft, and its efforts to provide a unified, risk-based regulatory approach for all diagnostic tests. There are several areas in which the discussion draft makes important improvements upon the Food and Drug Administration's (FDA) proposed LDT regulatory framework. The Society also supports the modernization of the Clinical Laboratory Improvement Amendments (CLIA) to provide improved oversight of laboratory operations. However, IDSA is concerned that the discussion draft may still lead to many of the

same problems we identified in our January 2015 comment letter regarding FDA's proposed LDT regulatory framework and ultimately, it could restrict patient access to high quality tests and threaten needed innovation of novel tests for constantly changing and emerging infectious diseases.

While IDSA welcomes the proposal's inclusion of a grandfather clause that minimizes disruption to tests currently in use, 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 transplantation medicine and 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, these same laboratories will still lack the financial and administrative resources for even one moderate risk premarket submission, let alone submissions for all new LDTs. It is also highly unlikely these laboratories would be able to navigate the high risk test premarket submission process.

Rather than continuing to develop innovative new LDTs, these laboratories will likely move to predominant or exclusive use of commercial diagnostics tests or send 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 that could be 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 met with LDTs. Lastly, commercial laboratories may lag significantly in making new tests available as new diseases emerge, putting patient safety and public health at risk.

Sending clinical specimens to reference laboratories for testing can significantly increase the turnaround time required to get the results to physicians. Rapid diagnostics that facilitate early initiation of life-saving treatment are critical in ID patient care, where even a few hours delay can significantly impact patient outcomes. Public health responses also require rapid identification of an emerging health risk, and any delay in activation of important public health protocol allows dangerous infections to spread. Delays incurred by sending specimens to reference laboratories with requirements for transport time and inflexible testing schedules may significantly impact detection of ID outbreaks

IDSA would like to offer several specific recommendations on the discussion draft below as well as express support for certain provisions.

Sec. 3. Regulation of In Vitro Clinical Tests

Single approach for commercial test developers and academic laboratories

IDSA strongly disagrees that large scale commercial entities should be regulated in the same way as academic clinical laboratories in how they design, validate, and use diagnostic tests because commercial tests are used in a much broader population than many LDTs. 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 high standards of validation necessary for such a commercial test scenario typically would not apply to small

academic laboratories that use their own LDTs only for their local hospital system or related community hospitals, and place undue burden on their ability to develop new innovative tests.

IDSA believes the discussion draft's proposed new definition of oversight will not solve the issues we have previously raised with the FDA's draft LDT regulatory framework. As stated above, academic clinical laboratories simply do not have the resources or infrastructure to undertake the discussion draft's premarket submission process for tests, which may limit patient access to the innovative tests needed to guide treatment of infectious diseases, particularly new diseases or those for which commercial laboratories do not yet offer a timely diagnostic.

IDSA recommends that the Committee consider allowing 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 CLIA laboratory operation oversight would provide appropriate regulatory functions.

Application of the Practice of Medicine (page 5, line 11—page 6, line 5)

IDSA appreciates the Committee's recognition that it would be inappropriate for the discussion draft to regulate the practice of medicine. However, we note that the discussion draft's definition of activities included under the term "practice of medicine" does not include the development, manufacture or running of a diagnostic test, including an LDT. It is unclear whether this exclusion could result in physicians being subjected to increased liability by performing these activities even as allowed by this discussion draft.

Low risk designation for all platforms (page 13 line 3-24)

The discussion draft proposes to consider all platforms, defined as both the instrument and the software needed to run a test, as low risk. IDSA is concerned that the definition of the software needed to run a test is unclear. For example, data sets are used for sequencing to identify human immunodeficiency virus (HIV) drug resistance or by Matrix Assisted Laser Desorption Ionization Time-of-Flight (MALDI-TOF) systems for bacterial and fungal identification. These database sets can have a significant impact on patient care, and IDSA does not consider these to be low risk should they be included in the proposal's definition of a platform. **IDSA urges the Committee to explicitly define what types of software are considered as part of a testing platform. 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 are assessed appropriately.**

Classification and reclassification processes

IDSA believes the discussion draft's risk based classification is a reasonable alternative to the FDA's LDT proposal and applauds its iterative aspect that would allow developers or the 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 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 are classified appropriately.

The definition of "well characterized" (page 20, line 13—page 21, line 3) includes several appropriate types of evidence. 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 is allowed under the discussion draft's definitions of risk. However, if the definition of "well characterized" is not described in more detail, we are concerned that the Secretary may be likely to take a very conservative approach to risk classification and inappropriately deem many tests as high risk. **Guidance to more explicitly define "well characterized" would allow for more informed evidence-based decisions on whether to lower a test's risk. We recognize it may be inappropriate to address this level of detail in statute, but recommend that the discussion draft direct FDA to provide guidance on this point.**

Premarket Review

IDSA appreciates the Committee's efforts to streamline the regulatory process for premarket submission of high and moderate risk tests, which we believe will allow patients to access innovative new ID diagnostics more quickly. The discussion draft requires that "reasonable assurance" of both clinical and analytical validity be determined, and indicates that the degree of evidence needed will vary and be based on a list of several appropriate sources of evidence (page 23, line 12—page 24, line 9). This list, while a promising start, is too vague to ensure consistent and robust oversight, as "reasonable assurance" could vary widely in practice and possibly result in the approval of tests with unacceptably high risk to patients. **IDSA urges the Committee to direct FDA to provide a more explicit, detailed definition of "reasonable assurance" to ensure these standards do not promote the development and approval of unsafe tests.**

In addition, the proposal uses the word "commercialization" for approved tests, a term that seems to cover commercial manufacturer tests that are marketed. Small academic centers do not commercialize their tests, and it is unclear whether the discussion draft would consider the term "commercialization" to include a laboratory developing a test for patient care within its own institution, health care system, or among related community hospitals and local physician practices**. IDSA recommends that the Committee consider using another term than commercialization, perhaps implementation, and clarify that its definition covers these activities undertaken by academic laboratories.**

Grandfathered tests (page 32, line 13—page 34, line 16)

IDSA greatly appreciates the grandfathering provision, which would allow LDTs developed and utilized prior to the enactment of the discussion draft to be deemed approved, as long as the developing laboratory notifies the Secretary of the test within 180 days of this bill's enactment. Under this section, laboratories would only need to provide readily available data in summary form and would not need to submit any application for premarket approval. Importantly, we also thank the Committee for making clear that laboratories would not be subjected to FDA user fees for providing notification regarding their existing LDTs. This provision would help limit the significant disruption to patient access to testing that would occur under the FDA's proposed LDT regulation, given that academic laboratories lack the financial and administrative resources necessary to submit PMA or 510(k) applications for all of their existing LDTs.

Premarket Requirements for Modifications (page 34, line 17—page 38, line 7)

IDSA applauds the proposal'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. The proposal further indicates that CLIA oversight would remain to verify the analytical validity for modifications that do not have meaningful clinical impact or change intended use, even if they use specimen types different from those for which the test was intended (page 68 line 22 – page 69 line 16). However, based on the language, it remains unclear what level of analyte alteration would actually change the intended use of the test and trigger review. For example, taking a cervical swab based test for Herpes Simplex Virus (HSV) and using it on cerebrospinal fluid (CSF) to test for more serious HSV encephalitis may arguably change the intended use based on the language, triggering costly FDA review given that herpes encephalitis is a very different form of disease than genital herpes. On the other hand, using a test designed for cervical *Neisseria gonorrhoeae* on rectal swabs would not change the intended use under the current language. **IDSA recommends that the discussion draft should clarify that all specimen type changes would not trigger FDA oversight, as long as analytical validation of the modification is confirmed by CLIA oversight.**

Priority Review Vouchers (page 38, line 8—page 40, line 15)

IDSA is pleased to support this section, which we hope will help incentivize the development of new tests for unmet medical needs, including emerging disease threats such Middle East respiratory syndrome coronavirus (MERS-CoV), avian influenza, hemorrhagic fevers, and vector borne diseases such as Dengue fever and Chikungunya.

Special Categories of In Vitro Clinical Tests

De-identified samples (page 41, line 10—page 42, line 8)

IDSA greatly appreciates that the discussion draft would explicitly not require an investigator to obtain informed consent for the use of de-identified human samples. Diagnostic development relies heavily on the use of clinical samples that are collected during routine standard of care and anonymized. A large number of samples from patients with varying characteristics (e.g., age, clinical condition, clinical setting) are needed to ensure that test results more accurately reflect a real-world patient population. Requiring informed consent would add considerable time and expense to anticipated studies, limiting the diversity of patient populations and the types of pathogens detected in studies.

Exception for rare diseases and conditions (page 43, line 5—page 45, line 21)

IDSA greatly appreciates that this proposal aligns with the 1983 Orphan Drug Act definition of rare diseases as those that affect fewer than 200,000 patients nationwide. This is a welcome difference from the FDA's LDT proposed regulatory framework, which instead would use number of times for which a disease is tested as the metric for determining if a disease is rare. In the field of infectious diseases, rare and common diseases often have very similar symptoms, and thus rare infectious must be tested for quite frequently. The discussion draft's regulatory pathway's premarket requirements are appropriate, given the difficulty for developers to establish the clinical validity of a test for a rare disease. However, IDSA is concerned that academic clinical laboratories would be extremely unlikely to have the ability to perform the postmarket data collection needed to establish clinical validity through this pathway. Given that

these same laboratories are the most likely developers of such tests for rare diseases, we believe this pathway's design will not improve, but hamper, patient access to tests for rare diseases, **While IDSA recommended above that all tests developed by academic 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, if that is not feasible, we recommend that at least all tests to diagnose rare diseases developed by academic laboratories for the uses described above be exempted from the new oversight proposed in the discussion draft.** Under such a scenario, analytic validation would still be required for these tests, and CLIA laboratory operation oversight would provide appropriate regulatory functions.

Exception for emergency use (page 45, line 21—page 47, line 12)
IDSA applauds the discussion draft's regulatory pathway to allow the rapid development and approval of tests during a public health emergency, and agree with the pathway's expedited premarket review process for tests receiving emergency use authorization (EUA). However, public health laboratories will likely play an active role in developing tests for public health emergencies, and will almost certainly not have the resources to perform the postmarket data collection needed to verify clinical validity. Also, for public health emergencies that do not rise to the level of an EUA, such as Chikungunya or multi-drug resistant microbial infections, academic and public health laboratories would simply be unable to navigate the regular premarket submission process. Similar to our concerns with the rare disease pathway, this pathway, as designed, could delay the development of and patient access to tests for new or emerging ID threats. **IDSA recommends that tests developed and/or used by public health laboratories be exempted from the new oversight proposed in the discussion draft.**

Exception for unmet need (page 47, line 13—page 48, line 7)
While we appreciate the inclusion of a regulatory pathway for tests for unmet need, we are disappointed to see that the pathway only specifies that these tests be regulated as moderate risk. Given how rapidly pathogens emerge and evolve, IDSA firmly believes that test developers should be given flexibility to swiftly develop tests for unmet needs. By requiring all developers, especially those in academic clinical laboratories, to submit premarket submission for these tests, IDSA is concerned we will limit access to testing for patients who have few or no alternatives to improve their care. Similar to our above comments, **IDSA recommends that all tests for unmet needs developed by academic 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 exempted from the new oversight proposed in the discussion draft.** Under such a scenario, analytic validation would still be required for these tests, and CLIA laboratory operation oversight would provide appropriate regulatory functions.

Sec. 4: FDA fees (page 65 line 21)
We see the discussion draft includes a placeholder section on FDA fees. IDSA is concerned that if clinical microbiology laboratories are forced 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 strongly urges that the Committee consider exempting clinical microbiology laboratories and public health laboratories from any FDA user fees.**

Both LDTs and commercial tests play important roles in the care of patients with infectious diseases, and IDSA reiterates 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 also offers the expertise of its members to assist the Committee in its efforts to develop a unified diagnostic regulatory framework. We look forward to working with the Committee to ensure that any new oversight activities will appropriately accommodate the ever-changing needs of timely test development. Should you have any questions or concerns about these comments, please feel free to contact Amanda Jezek, IDSA Vice President for Public Policy and Government Relations at ajezek@idsociety.org or 703-740-4790 or Greg Frank, PhD, IDSA Program Officer for Science and Research Policy, at gfrank@idsociety.org or 703-299-1216.

Sincerely,

Stephen B. Calderwood, MD, FIDSA
IDSA President

About IDSA

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 pneumoni*ae, 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.