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November 12, 2015

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

The Honorable Joe Pitts
Chairman
Subcommittee on Health
420 Cannon House Office Building
Washington, DC 20515

The Honorable Frank Pallone, Jr.
Ranking Member
Energy and Commerce Committee
237 Cannon House Office Building
Washington, DC 20515

The Honorable Gene Green
Ranking Member
Subcommittee on Health
2470 Rayburn House Office Building
Washington, DC 20515

Dear Chairmen Upton and Pitts and Representatives Pallone and Green,

The Infectious Diseases Society of America (IDSAs) is pleased to offer the Committee comments on the second discussion draft to establish a regulatory framework for both *in vitro* diagnostic tests and laboratory developed tests (LDTs). We also thank you for scheduling the subcommittee hearing entitled, "Examining the Regulation of Diagnostic Tests and Laboratory Operations," on November 17. We appreciate the Committee's close attention to these important issues, which have significant implications for patient care and public health.

Infectious diseases (ID) physicians care for patients of all ages with serious, often life-threatening, infections. They rely upon diagnostics, both commercial tests and LDTs, to identify the pathogen causing an infection and its antimicrobial drug susceptibility, enabling the rapid application of appropriate treatment to improve patient outcomes. ID diagnostics also play a critical role in enabling public health officials to rapidly respond to and contain outbreaks. Lastly, ID diagnostics are vital for guiding clinicians' stewardship of antimicrobial drugs to limit the development of resistance—a topic for which we are grateful that this Committee has paid a great deal of attention.

IDSAs recognizes that there are valid concerns about the risks associated with LDTs, particularly in areas such as cancer and genetic testing. 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, IDSAs believes the risks raised by the use of ID LDTs are dwarfed by their advances and benefits to patient care. Therefore, it is critical that any steps taken by Congress or federal agencies to alter the regulation of LDTs appropriately balance the need for increased oversight with the need to maintain and enhance innovation and patient access to state-of-the-art testing.

Given the important role of diagnostics in ID patient care, IDSA has been highly engaged in the ongoing policy discussions regarding LDT regulation, providing [comments on the draft FDA regulatory framework](#), [responding to the Committee's white paper](#) and [previous discussion draft](#), and also endorsing [a proposal put forward](#) by the Association of Molecular Pathologists (AMP).

IDSA welcomes the second discussion draft and acknowledges that it makes several key improvements upon the first discussion draft and the Food and Drug Administration (FDA) LDT proposed regulatory framework. However, our Society remains concerned that the discussion draft may still lead to many of the same problems we previously identified with the FDA proposal and first discussion draft. In particular, the proposed new regulatory requirements for premarket review of LDTs would likely still be prohibitive for clinical laboratories in the hospital setting, thus severely limiting innovation of novel LDTs for emerging and evolving infectious diseases and curtailing patient access to testing.

While IDSA appreciates 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 test 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 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 that can be covered by LDTs. Those commercial tests that are available are often more expensive and may require investment in new instruments from multiple manufacturing 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 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 delay detection of ID outbreaks.

IDSA would like to offer several specific questions, concerns, and recommendations on the new discussion draft below as well as express support for certain provisions. If the Committee opts to advance this discussion draft, we hope our recommendations will be useful in your endeavors. However, we also urge the Committee to consider an alternative approach—enhancing the regulation of LDTs primarily through Clinical Laboratory Improvement Amendments (CLIA) modernization. Following our comments on the discussion draft, IDSA will briefly share our thoughts about why we believe an approach focused on CLIA modernization is the most appropriate and feasible mechanism for strengthening LDT oversight while preserving patient access to testing and promoting innovation.

Sec. 3. Regulation of In Vitro Clinical Tests

Public Health Surveillance Exemption

IDSA is pleased to see that the second discussion draft includes a new provision to exempt public health surveillance from the newly proposed regulations. We strongly agree that surveillance is essential to maintaining public health responses, and we support excluding tests with these uses from oversight. **We believe this exemption should apply only to tests used by public health laboratories, and urge the Committee to make this clear in the discussion draft.**

Single approach for commercial test developers and academic laboratories

In our comments on the Committee's first discussion draft, IDSA strongly opposed regulating large scale commercial entities in the same manner as academic clinical laboratories in how they design, validate, and use diagnostic tests. 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 would place an undue burden on their ability to develop new, innovative tests.

We appreciate that the second discussion draft describes its proposed premarket review process in more detail. However, we remain extremely concerned that the second draft still does not adequately address the issues IDSA previously raised with the first discussion draft and the FDA draft regulatory framework, namely that academic clinical laboratories do not have the resources necessary to navigate the premarket review process. As a result, IDSA remains concerned that the second discussion draft would still severely curtail the ability of academic clinical laboratories to develop and utilize LDTs, in turn seriously limiting patient access to innovative tests needed to guide optimal patient treatment.

IDSA again 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.

Low risk designation for all platforms (page 10, lines 23-25, page 11, lines 1-3, and page 21 lines 8-15)

The second discussion draft proposes to consider all platforms, defined as both the instrument and the software needed to run a test, as low risk. IDSA remains 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 and fungal identification. It is unclear if the second discussion draft would include such databases in the definition of software. These database sets can have a significant impact on patient care, and IDSA does not consider them low risk. **IDSA urges the Committee to more explicitly define what types of software are considered 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 can be assessed appropriately.**

Classification and reclassification processes

In general, IDSA believes the second 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 second 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.

IDSA also recognizes the appropriateness of considering "mitigating factors" (page 16, lines 1-13) 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 is allowed under the second 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 more rapid patient access to innovative new ID diagnostics. The second discussion draft requires that "reasonable assurance" (page 38, line 24—page 39, line 3) of both clinical and analytical validity (defined on

page 8, lines 5-25) be determined. IDSA appreciates that this discussion draft (unlike the first) includes explicit definitions of clinical and analytical validity. IDSA also appreciates that the second discussion draft includes more explicit language to define what may constitute the “valid scientific evidence” that must be presented in a test’s premarket approval application (page 12, line 7—page 13, line 11). However, we remain concerned that the term “reasonable assurance” 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.**

IDSA appreciates that the second discussion draft no longer uses the word “commercialization” for approved tests. As we pointed out in our comments on the first discussion draft, small academic centers do not commercialize their tests, and use of that term caused uncertainty and unease regarding what activities would be covered by the proposal.

Premarket Requirements for Modifications (page 65, line 22—page 73, line 9)

IDSA applauds the second 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. IDSA is 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. This would allow, for example, the use of a test designed for cervical *Neisseria gonorrhoeae* to be used on rectal swabs, as such a specimen change would not alter the intended use of the test.

Special Pathways for Certain Tests

IDSA appreciates that the second discussion draft includes revised language regarding the regulatory exemptions for special 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 3 year postmarket obligation provides the FDA and a developer more flexibility in establishing a balanced plan that satisfies clinical validity for a test while ensuring patient access to innovative testing.

IDSA also again appreciates that the Committee would not explicitly require an investigator to obtain informed consent for the use of de-identified human samples. 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 55, line 16—page 56, line 15)

The second discussion draft no longer defines rare diseases as those that affect fewer than 200,000 patients nationwide (the definition used by the Orphan Drug Act), instead using an incidence of 8,000 patients a year nationwide, or a prevalence of 50,000 patients total. While this change is less restrictive than the FDA’s proposed definition based on number of tests

performed nationwide, we are concerned that this 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 would appreciate clarification regarding why the Committee pursued this change and how it arrived at the currently proposed definition.**

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, 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.

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 be exempt from additional oversight. If oversight discretion in these instances 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

IDSA is disappointed to see that no explicit special category has been retained in the second discussion draft for the rapid development and approval of tests during public health emergencies. While we had concerns with the exemption as designed in the May 2015 discussion draft, we applauded the Committee's decision to include a pathway to ensure appropriate public health responses to outbreaks. **IDSA recommends that that the exemption for tests developed in response to public health emergencies be reconsidered for inclusion in the second discussion draft. Given the key role public health laboratories play in outbreaks, IDSA again recommends that any tests developed and/or used by public health laboratories be exempted from the new oversight proposed in the discussion draft.**

Sec. 4: FDA fees (page 65 line 21)

The second discussion draft again includes a placeholder section on FDA user fees. IDSA remains 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.**

An Alternative Approach: Strengthening the Regulation of LDTs through CLIA Modernization

IDSA greatly appreciates the Committee's efforts to provide an alternative to the FDA's proposed LDT regulatory framework and to improve upon the first discussion draft, and we believe the second discussion draft contains some important provisions to streamline the regulation of commercial tests that will improve patient access to this type of important testing. However, we continue to believe that regulating LDTs and commercial tests in the same manner is inappropriate, given the substantial differences in how these tests are used. Further, we remain concerned that any proposal that would shift the bulk of LDT regulation from CLIA to the FDA would pose largely insurmountable hurdles to academic laboratories, ultimately impeding patient access to existing high quality tests and threatening needed innovation in the development of novel tests to keep pace with constantly changing and emerging infectious diseases.

Earlier this year, IDSA was pleased to endorse a proposal put forward by AMP to enhance LDT regulation by modernizing CLIA oversight of labs to include clinical validity of LDTs in addition to its current regulation of analytical validity. We understand this proposal is receiving close consideration by several members of the Senate Health, Education, Labor and Pensions Committee. As academic clinical laboratories are already familiar with CLIA, this approach will likely be far less disruptive to patient access to testing. Further, the AMP proposal includes a refined risk classification that appropriately categorizes ID tests. It also expands the types of evidence accepted to demonstrate clinical validity, including the use of peer reviewed data and clinical guidelines, reducing the financial and administrative burden for laboratories. The proposal appropriately addresses test modifications to ensure that minor changes are only subject to analytical validity assessment during regular inspections, while major changes are reviewed before use in patient care. Finally, the proposal provides regulatory exemptions to ensure testing for public health emergencies is unimpeded. IDSA believes this proposal enables appropriate regulatory oversight of LDTs while also minimizing the disruption of patient access to novel ID testing.

While the AMP proposal has some outstanding issues (including the need to refine the public health exemption, clarify the quantity of data needed to establish clinical validity, and the elimination of uncertainty in the deadline review process), IDSA is confident that CLIA modernization represents the more feasible and appropriate mechanism for enhancing LDT regulation while preserving patient access to high quality testing and fostering innovation of new tests. **We strongly encourage the Committee to closely review the AMP proposal and consider using it as a guide for legislation to enhance the regulation of LDTs.**

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 improve the regulatory environment for diagnostics. 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,

A handwritten signature in black ink that reads "Johan S. Bakken MD, PhD". The signature is written in a cursive, slightly slanted style.

Johan S. Bakken, MD, PhD, 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 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.