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Infectious Diseases Society of America

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Submitted electronically to cures@mail.house.gov

RE: 21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests

Dear Chairman Upton and Representative DeGette:

The Infectious Diseases Society of America (IDSAs) thanks the Committee for this opportunity to comment on the 21st Century Cures request for feedback, “A Modernized Framework for Innovative Diagnostic Tests.” IDSAs welcomes the Committee’s interest in the recently released FDA framework for regulating laboratory developed tests (LDTs) as well as the Committee’s broader commitment to incentivizing the development and clinical integration of innovative diagnostic tests.

IDSAs recognizes that there are valid concerns about the risks associated with LDTs in areas such as cancer, genetic testing, as well as infectious diseases. While many infectious disease (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. Unlike other disease areas, the evidence that the ID LDTs provide unreliable results that lead to harmful patient care decisions is lacking.

IDSAs is very concerned that LDT oversight, as currently proposed by the Food and Drug Administration (FDA), could impede patient access to existing high quality or state of the art tests and may curtail the development of novel tests for emerging infectious diseases. We are pleased to offer recommendations to help ensure that appropriate patient access to ID LDTs is maintained, and we will also share these recommendations with the FDA at the agency’s January workshop on this topic as well as in a formal comment letter. We look forward to continuing to work with the Committee on these important issues.

IDSAs 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 infections such Ebola virus, enterovirus D68, Middle East Respiratory Syndrome Coronavirus

(MERS-CoV), and bacteria producing the New Delhi metallo-beta-lactamase (NDM) enzyme that makes them resistant to a broad range of antibacterial drugs.

Over the past several years, IDSA has stressed the importance of innovative diagnostic devices for the care of patients suffering from infectious diseases, most notably in our 2013 report, [Better Tests, Better Care: Improved Diagnostics for Infectious Diseases](#). Improved diagnostics 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. Below IDSA is pleased to respond to key questions posed by the Committee:

3. FDA intends its regulation of diagnostics to be risk-based. How should risk be defined? Are the types of risks posed by diagnostic tests different from therapeutic medical devices? Are these risks different with LDTs compared to distributed test kits? Is the traditional medical device classification system appropriate for these products?

Multiple factors may be considered when defining risk. IDSA recommends that the FDA consider past and present uses of LDTs, recognize different patterns of use in different disease areas, and document both harm and benefits that LDTs contribute to patient care. The FDA should balance the risk associated with current use of LDTs in each relevant disease area against the risk of curtailing patient access to LDTs under the proposed regulations. 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.

In its regulatory framework, the FDA has prioritized oversight of high risk LDTs for “certain infectious diseases with high-risk intended uses,” notably viral load tests for cytomegalovirus. These LDTs have been in use for many years by laboratories, with well-documented data demonstrating clinical validity and peer reviewed literature supporting their use. In many instances, these LDTs have become the standard of care. Given their longstanding use and significant supporting data, **IDSA asserts that tests for transplantation-related viruses do not pose a high risk to patients and should be reclassified as moderate risk tests. IDSA offers the expertise of its members to assist in this process.**

5. Are there areas where the balance between pre-market review versus post-market controls should be reconsidered? How can post market processes be used to reduce barriers to patient access to new diagnostic tests?

Earlier in 2014, FDA issued a pair of guidance documents on this issue, entitled, “Expedited Access for Premarket Approval of Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions,” and “Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval.” IDSA applauded these guidances for taking steps to speed patient access to urgently needed diagnostic tests, and **we recommend that FDA extend this level of flexibility to LDTs that it intends to regulate.**

For medical devices addressing unmet medical needs, greater uncertainty about the benefit-risk profile of the device should be accepted and by shifting data collection from the pre-market to post-market phase, urgently needed life-saving devices can reach patients more rapidly. For a patient with a serious or life-threatening infection that cannot be identified in a sufficiently rapid manner to substantively impact care and outcomes, FDA must appropriately weigh the risk of approving a new diagnostic test based upon a smaller premarket data set against the risk of not having urgently needed new diagnostics.

There are several important infectious disease areas for which it is extremely challenging to collect large quantities of pre-market data due to the rare occurrence of certain diseases, such as viral encephalitis or invasive fungal infections. This challenge can hamper the development of both commercial diagnostics and LDTs. In such instances, allowing approval of tests based upon smaller premarket data sets and facilitating collection of postmarket data can allow urgently needed tests to reach patients while the utility of using these tests continues to be studied in clinical settings.

6. A number of stakeholders have expressed concerns about uncertainty as to when a supplemental premarket submission is required for a modification. When should they be required prior to implementing modifications? Should the requirements for submission of a supplemental clearance or approval differ between LDTs and distributed test kits?

When manufacturers make improvements to tests, the process that has been created to speed the clearance of the modified test is extremely important to improving access to testing. For example, when adding an emerging pathogen to a multiplexed test, it is expected that a comprehensive analytical validation will be completed. **Allowing a more limited clinical trial to be performed focusing on the new pathogen would make the test available to clinical laboratories in a more rapid manner.** Given how rapidly pathogens emerge and evolve, lack of frequent updates is particularly problematic in the area of infectious diseases and a key factor in the need for continued flexibility in this disease area.

Finally, the FDA has indicated that if a commercial test is used on a specimen other than what was originally intended, that test would be considered an LDT subject to oversight. **IDSA argues the need to test these non-intended specimens represent an unmet medical need.** For example, if a commercial diagnostic can identify a given pathogen in serum, but there exists a need to test cerebrospinal fluid (CSF) for the same pathogen, the use of an analytically verified LDT to test CSF for this pathogen should be subject to oversight discretion.

9. How should any regulatory system address diagnostic tests used for rare diseases or conditions, customized diagnostic tests and diagnostic tests needed for emergency or unmet needs (e.g. Ebola)?

The FDA currently use the Humanitarian Use Devices (HUD)/Humanitarian Device Exemption (HDE) to define diagnostics for rare diseases as those for which no more than 4000 tests are performed each year nation-wide. Rare infectious diseases present some unique challenges to the FDA's current definition. Rare infections, such as encephalitis caused by herpes simplex virus (HSV) and varicella zoster virus (VZV), or invasive aspergillosis have symptoms that are

also common in more widespread infections. In order for these rare infections to be ruled out, they must be tested for at far higher rates than the FDA limit of 4000/year nationwide.

The Center for Drug Evaluation and Research (CDER) at the FDA defines rare diseases, based on the 1983 Orphan Drug Act, as those that affect less than 200,000 patients nationwide. **IDSA proposes that the LDT regulatory framework align with this definition to permit oversight discretion for LDTs for diseases with less than 200,000 patients in the United States.** In addition, pathogens can cause both common and rare diseases; for example, herpes encephalitis is a rare disease, while genital herpes infection and fever blisters are much more common. **IDSA recommends that the FDA not constrain its definition of a rare disease based on the pathogen, but rather on the disease itself.**

For LDTs that address unmet medical needs, IDSA has concerns over the regulatory framework the FDA has proposed when a commercial test meeting this need is approved. **IDSA does not believe the 12-month period laboratories are given to submit to the FDA or switch to the commercial test is sufficient, and recommends at least a 2-year phase-in period.** Most clinical microbiology laboratories operate under a 12-month capital upgrade cycle, and depending on when a commercial test is approved, would not likely be able to purchase the equipment needed for a test within the 12-month period, resulting in situations where laboratories may lose the capability to conduct any testing for critical unmet medical needs.

IDSA also urges the FDA to delay regulatory oversight of LDTs for unmet medical needs until several commercial tests are approved. With only one option, laboratories may be forced to purchase expensive equipment that may be used for only one test. Delaying regulatory oversight of LDTs for unmet medical needs until several commercial tests for the unmet medical need are approved will give laboratories much needed flexibility to choose tests appropriate to their space and cost limitations. Moreover, while the vast majority of FDA-approved and cleared tests have excellent performance characteristics, there are clear instances of tests that identify viral resistance mutations in which LDTs have superior performance characteristics compared to commercial tests. Delaying enforcement until multiple commercial tests are approved will assist laboratories in addressing these issues.

11. What incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests?

IDSA proposes several policies to directly support the development of new diagnostic tests as well as to encourage their appropriate use, which benefits patient care and helps ensure a market for these products. Below is an overview of policies IDSA believes could be incorporated into the 21st Century Cures initiative, which we also discussed in our May 30 letter to the Committee in response to the first 21st Century Cures white paper.

Public Private Partnerships: **Direct the Department of Health and Human Services (HHS) to establish a public private partnership (PPP) similar to the European Rapid Point-of-Care test Platforms for Infectious Diseases (RAPP-ID) program and to include diagnostics in the new biopharmaceutical incubator announced as part of the [National Strategy for Combating Antibiotic Resistant Bacterial \(CARB\)](#).** In 2011, the European Commission (EC) [launched RAPP-ID](#), a PPP bringing together government experts, academia and industry aimed

at developing fast and reliable point-of-care tests for the detection of various pathogens. In the U.S., Biomedical Advanced Research Development Authority (BARDA) currently partners with companies on diagnostic R&D, but BARDA does not currently bring together multiple companies with government and academic experts to collaborate and share information.

Biorepositories: **Direct the National Institute for Allergy and Infectious Diseases (NIAID) to examine opportunities to support the development of virtual biorepositories for viruses, fungi and other pathogens, utilizing samples already being collected for research, similar to the existing bacteria virtual biorepository. Provide incentives and support for institutions to save de-identified specimens and to participate in virtual biorepository catalogues.** A key challenge in clinical trials for new diagnostics is access to clinical samples, particularly those containing rare pathogens. The Antibacterial Resistance Leadership Group (ARLG), a research team funded by NIAID, established a [Virtual Biorepository \(VB\) Catalogue](#), a searchable, web-based system that provides researchers with unique access to clinically well-characterized bacteria for the development of diagnostic tests and other research. The bacteria are housed at multiple locations. This approach requires significantly less resources than traditional physically centralized biorepositories.

Conflict of Interest: **Clarify that institutions receiving federal funding should implement conflict of interest (COI) policies that appropriately enable transparent industry/institutional research collaborations.** Often expert input or independent validation of a potential test is needed during development. Institutional COI policies are often much more strict than the National Institutes of Health (NIH) [COI regulatory framework](#), which was intended to provide guidance to institutions on how to manage COI. Unfortunately, institutional COI policies often bar those best suited for these activities, sometimes even if the expert is willing to work for free on his or her own time. This forces developers to forgo expert input or use laboratories lacking expertise for independent testing. This loss of expert input and the resources diverted to train and supervise testing at labs lacking expertise can add considerable time and cost to diagnostic development.

Physician education programs on the utility of new diagnostics: **Direct the Agency for Healthcare Research and Quality (AHRQ), specifically through its Center for Evidence and Practice Improvement (CEPI), to conduct or support research to demonstrate the impact of new ID diagnostics on patient care and outcomes, and to disseminate the results of that research to physicians to encourage them to appropriately utilize new diagnostics.** Many physicians and other health care providers may be hesitant to use new diagnostic tests, in part because they are often uncertain of how best to integrate them in their practice and how to interpret results. Little guidance currently exists on the use of diagnostic tests for a particular type of infection, or what bundles of tests should be used if a patient has a particular set of symptoms. The ability to construct useful guidelines is hampered by the lack of clearly designed outcomes studies demonstrating patient benefit when tests are used as part of clinical decision making. CEPI is well-suited to address this need, as the Center is tasked with conducting and supporting research on health care delivery and improvement and advancing decision and communication sciences to facilitate informed treatment and health care decision making by patients and their health care providers.

Again, IDSA thanks you for opportunity to provide comments on this important topic. Should you have any additional questions, please contact Jonathan Nurse, IDSA's Director of Government Relations, at jnurse@idsociety.org or 703-299-0202.

Sincerely,

A handwritten signature in purple ink that reads "Stephen B. Calderwood". The signature is written in a cursive, flowing style.

Stephen B. Calderwood, MD, FIDSA
IDSA President