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IDSA
Infectious Diseases Society of America

August 20, 2018

The Honorable Larry Bucshon, MD
United States House of Representatives
1005 Longworth House Office Building
Washington, DC 20515

The Honorable Diana Degette
United States House of Representatives
2111 Rayburn House Office Building
Washington, DC 20515

Dear Representatives Bucshon and DeGette:

The Infectious Diseases Society of America (IDSA) appreciates the opportunity to offer feedback on the August 3 Food and Drug Administration (FDA) comments on the draft Diagnostic Accuracy and Innovation Act (DAIA), which builds upon previous efforts to establish a modern framework for the regulation of *in vitro* diagnostic tests (IVDs) and laboratory-developed tests (LDTs). We look forward to sharing our perspective on the important role of infectious disease (ID) LDTs in clinical care and public health and the potential impacts of the proposed regulations on innovation and patient access to testing.

IDSA remains concerned that the current FDA proposal to regulate LDTs and IVDs as a single category known as *in vitro* clinical tests (IVCT) will negatively affect public health and patient care for infectious diseases. It is imperative that any legislation on this complex issue reflect balanced input from diverse affected stakeholders. Most importantly, it should serve the best interests of patients who need access to high-quality, rapid testing. Currently, neither the DAIA draft nor the FDA technical assistance (TA) document reflect stakeholder consensus. Both documents favor the interests of commercial manufacturers and vendors over the concerns of ID clinicians and academic clinical laboratories.

We appreciate your close attention to this multifaceted issue and look forward to working with you to craft appropriate policies that spur desired innovation and protect patient access to high-quality diagnostic testing.

Please find several specific questions, concerns, and recommendations in response to the August 2018 FDA TA document below. We hope our feedback will be useful. We would greatly appreciate the opportunity for continued dialogue with FDA and Congress on this important issue.

Background:
ID physicians care for patients of all ages with serious, often life-threatening infections. Time is of the essence in ID patient care, where even a few hours' delay in reaching a diagnosis can negatively impact patient outcomes. To

rapidly administer appropriate treatment for infectious illnesses, physicians rely on laboratories to provide clinically relevant diagnostic test results that identify the cause of infection and guide therapeutic selection. In-house testing is especially important at major medical centers that specialize in transplantation and the management of complex, critically ill patients, where physician and clinical laboratory scientists regularly develop and validate LDTs to keep pace with newly emerging diseases and offer diagnosis for less common pathogens that do not have FDA-approved commercial testing. ID diagnostics also help protect the broader public health by alerting health officials to the need for protocols to contain outbreaks and prevent the transmission of ID. Lastly, these tests are vital for guiding successful antimicrobial stewardship that limits the emergence of drug resistance and enhances hospital infection prevention.

Well-vetted ID LDTs have been used to diagnose and manage a variety of infectious diseases for over two decades. While IVD test kits are available for some pathogens and disease states, commercial assays are not yet available for the entire range of testing currently covered by LDTs. Commercial manufacturers may also lag significantly in developing tests for emerging or low-incidence diseases, leaving a gap that, if not filled, puts patient safety and public health at risk. Notably, sending clinical specimens to reference laboratories for testing will significantly increase the turnaround time required for physicians to receive results. Rapid diagnostics that facilitate early initiation of life-saving treatment are critical in ID patient care, where same-day results can significantly improve patient outcomes.

An additional limitation of commercial tests is cost. LDTs are often specifically designed for high-level and accurate performance on consolidated and standardized instrumentation in an individual laboratory. In contrast, commercial tests often 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.

Our Society has stressed the importance of innovative diagnostic devices that support the care of patients suffering from infectious diseases, most notably in the 2015 IDSA report, Better Tests, Better Care: The Promise of Next Generation Diagnostics. Given the important role of diagnostics in ID patient care, IDSA has been highly engaged in the ongoing policy discussions regarding LDT regulation. Our Society has provided comments on the 2014 FDA draft guidance, responded to a 2015 House Energy and Commerce Committee discussion draft, published a joint position paper on LDTs, offered a statement following the 2016 Senate Health, Education, Labor and Pensions Committee hearing on LDTs, responded to the FDA January 2017 discussion paper, and commented on the DAIA discussion draft as well as on FDA's April 2018 narrative TA document.

IDSA agrees that increased regulation of LDTs is needed to ensure safety and effectiveness in certain high-risk cases across different areas of medicine, but there are no data to support the FDA assertion that the categories of ID LDT targeted in the TA document run a high risk of harm. ID LDTs are required to be rigorously validated and performed under a system of regulations by the College of American Pathologists (CAP) and the Clinical Laboratory Improvement Amendments (CLIA). Analytical validation of laboratory developed tests requires a number of standardized measurements that ensure quality and reliability, such as accuracy (reliability and reproducibility of test results); precision (reproducibility); sensitivity

(limits of detection); and specificity (correctly identifying the target of interest). The validation data collected by these laboratories are subject to ongoing peer review.

We are extremely concerned that the proposed regulations will impede patient access to existing high-quality testing and threaten the innovation needed to keep pace with constantly changing and emerging pathogens. Commercial developers are not the best or only test innovators; it is critical that academic medical centers and not-for-profit laboratories remain unencumbered by prohibitive regulatory pathways that favor industry manufacturers and the largest reference laboratories. The long-term consequences of LDT regulation as currently proposed could be an anticompetitive environment in which only large regional for-profit commercial reference laboratories offer broad LDT test menus that are currently available in many medical centers.

Single approach for commercial test developers and clinical laboratories

As stated in our prior comments, IDSA strongly opposes regulating clinical and other not-for-profit laboratories in the same manner as large-scale commercial entities. We remain extremely concerned that neither DAIA nor the FDA TA adequately addresses the issues that we previously raised with the earlier discussion drafts and draft regulatory framework – namely, that **clinical and not-for-profit laboratories are not developing tests for a commercial market.**

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. The FDA TA document suggests that any IVCT offered for clinical use are deemed to be introduced into interstate commerce for purposes of regulation [(1)(B)], despite the substantial contingent of tests developed with no intention of commercial use. This sets up a false equivalence between LDTs and commercial test kits to the detriment of patients and clinical laboratories that rely on custom tests. Furthermore, unlike commercial test kits, ID LDTs are not generally assigned specific CPT codes and therefore may not be reimbursed at the same level.

While it is customary that for-profit manufacturers have dedicated regulatory affairs departments, clinical laboratories and academic medical centers typically lack these departments and the financial resources to create additional staff positions. **Moving to a manufacturer-based (vs. patient-centered) regulatory process, as the TA proposes, will cause substantial delays in processing ordered patient tests and severely limit access to testing, lengthen hospital stays, and worsen patient care.** Further, we are concerned that FDA likely lacks the capacity and third-party reviewer infrastructure to enforce its proposed legislation in a timely fashion.

LDTs for ID Pathogens Need an Appropriate Prioritization and Classification of Risk

A straightforward mechanism to classify the risks of LDTs is critical. **IDSA recommends that Congress and FDA consider present uses of LDTs, recognizing patterns and history of use and balancing risks in the relevant disease areas against the harms if the test is curtailed.** For example, many ID LDT results are used in combination with an assessment of clinical signs and symptoms, diagnostic imaging, and results of other tests to inform patient management decisions. **The vast majority of ID LDTs are not used as stand-alone tests, and this reduces the inherent risks of erroneous or misleading results.**

Despite longstanding FDA concerns regarding high-risk oncology and genetic tests, these disease areas are not discussed in the August 2018 technical assistance document. Nonetheless, FDA has specifically proposed excluding *in vitro* clinical tests used for HIV testing and transplant

patients, which would include tests for cytomegalovirus (CMV) and viral load testing for Epstein-Barr, BK virus, HHV6, adenovirus, and others from the precertification pathway. The rationale for these exclusions is unclear and in opposition to the risk-based framework of the document. The FDA recommendation is a major concern in light of the prohibitive costs of premarket submissions and potential impacts on patient care.

LDTs for transplant viral load testing have been in regular use for decades, with well-documented data demonstrating clinical validity supporting their use in peer-reviewed literature. In many cases, these LDTs have become the standard of care, and their use is recommended in multiple professional guidelines. It is critical to note that tests for serious or life-threatening infectious diseases may only carry moderate risk, which was allowed under previous drafts in the definitions of risk. **IDSA has long advocated that LDTs with proven safety, efficacy, and validity data – such as transplant viral load tests – should be included in any legislative exemption language. In 2016, the FDA Microbiology Panel of the Medical Devices Advisory Committee proposed that transplant viral load tests be down-classified from Class III to Class II, or moderate risk.** We urge FDA to complete the down-classification process as soon as possible to increase opportunities for developmental innovation and ensure that these tests are removed from high-risk consideration and eligible for proposed precertification pathways.

Sec. 587A. Applicability

Grandfathered IVCTs

IDSA strongly cautions the federal government against adopting policies that will severely limit the ability of clinical laboratories in academic medical centers to develop and use LDTs. While we appreciate the inclusion of a grandfather clause that minimizes disruption to tests currently in use, we are concerned that new test development needed to keep pace with rapidly changing ID threats will be hindered, particularly at major medical centers that specialize in the management of complex, critically ill patients. The vast majority of academic medical centers and not-for-profit clinical laboratories do not have the resources necessary to navigate the premarket review process. This would severely curtail the ability of laboratories to develop novel LDTs, thereby seriously limiting patient access to innovative tests.

Exemptions for manual tests

The FDA TA proposes exemptions for *in vitro* diagnostics that are designed, manufactured, and used within a single CLIA-certified laboratory. **IDSA recommends the expansion of the exemption criteria to include 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.** This expansion would reflect the appropriate, longstanding use of LDTs and maintain access to what is often the most rapid form of testing. 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.

Exemptions for rare disease

The FDA TA document defines rare diseases as those with an incidence of 8,000 patients a year nationwide and proposes exemptions for IVCTs that fit these criteria. However, there are many infectious diseases with an incidence above 8,000 that are still sufficiently rare that few or no commercial testing options exist. The FDA Center for Drug Evaluation and Research (CDER) defines rare diseases as those that affect fewer than 200,000 patients nationwide, based on the

1983 Orphan Drug Act. IDSA proposes that the LDT regulatory framework aligns with this definition to permit continued enforcement discretion for LDTs for diseases with fewer than 200,000 patients in the United States.

We are also deeply concerned that FDA has proposed excluding IVCTs for communicable diseases from receiving rare disease review exemptions. This exclusion would impede innovation in areas where well-characterized diagnostics are urgently needed. **We request that FDA clarify their rationale for this proposal and reconsider the unfounded assertion that LDTs for rare infectious diseases pose a greater risk than those for non-communicable illness.**

LDTs combat antimicrobial resistance and enable successful stewardship programs

We greatly appreciate the Energy and Commerce Committee's longstanding leadership in efforts to combat antibiotic resistance and are concerned that the current legislative proposals would impede clinical test development and have a chilling effect on hospital efforts to guide appropriate antibiotic use. Many LDTs are the first line of defense against antimicrobial resistance and help physicians determine appropriate antibiotic stewardship plans. One recently developed, first-of-its-kind test differentiates standard chlamydia strains that require one week of antibiotics from the more severe Lymphogranuloma venereum (LGV) type that requires three weeks of treatment. The test is an important factor in determining the treatment and ensuring appropriate antibiotic use for countless patients.

Some laboratories have also developed rapid diagnostics that screen for antimicrobial resistance to certain organisms (e.g., *Mycoplasma genitalium* resistance). One clinical laboratory recently developed a first-in-class test for hepatitis C virus that can accurately assess the efficacy of certain drugs for antiviral treatment, thereby allowing therapy to be tailored for the patient as well as improving the likelihood of successful patient outcomes while reducing the chances of resistance and recurrence. It is critical that clinical laboratories continue to be able to develop rapid diagnostic tests in response to patient needs and rare communicable diseases. **Such efforts may lead to interest in developing larger scale, commercial tests by companies that may not have sufficient research and development resources.**

Priority review, custom IVCTs, and exemptions for unmet needs

While we appreciate the inclusion of exemptions for custom and low-volume tests to meet unmet needs, we disagree with the proposed definition of custom tests as those "not included in a test menu, template test report, or other promotional materials, and not otherwise advertised." Often there may be a single commercial IVD on the market for a lesser-known disease, but with only one option laboratories may be forced to purchase expensive equipment to be used for only a single test if it is not performed on a platform they currently use. 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 with IVDs[1]. **We strongly recommend that at least two commercial IVDs be available to optimize laboratory uptake to preclude a categorization of "custom IVCT."**

As written, the TA provides a second pathway for the development of custom tests that appear to be exempt from premarket regulatory requirements provided that the test is "developed in order

[1] Kaul KL, Sabatini LM, Tsongalis GJ, et al. The Case for Laboratory Developed Procedures: Quality and Positive Impact on Patient Care. Academic Pathology. 2017;4:2374289517708309. doi:10.1177/2374289517708309.

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.

Similarly, we recommend that the criteria for IVCTs eligible for priority review (Sec. 587C) be expanded to include up to two approved or precertified alternatives to accommodate for clinical laboratory budget and space constraints while preserving patient access to care.

Public health surveillance exemptions

We are pleased to see that this assessment includes a provision to exempt public health surveillance activities from the proposed regulations. However, the FDA TA proposes that public health surveillance exemptions be extended to tests "intended solely for use on systematically collected samples for analysis and interpretation of health data essential to the planning, implementation and evaluation of public health practice, where such practice is closely integrated with the dissemination of these data to public health officials and linked to the prevention or control of disease or other public health threat." An *in vitro* clinical test that is either intended for use in making clinical decisions for individual patients or other purposes would not be considered exempt.

This definition limits the practice of public health to a fraction of its standard scope and discounts patient care entirely. In cases of localized emerging outbreaks that may not necessarily meet the criteria for an Emergency Use Authorization, it is essential that well-validated tests make their way to public health officials as expediently as possible. LDTs can often be developed quickly to help combat emerging outbreaks (e.g., H1N1) and support state reference laboratories for decreased test turn-around time. Further, these results are frequently critical in informing clinician decisions for patient care.

Sec. 587D. Precertification

IDSA agrees that a precertification pathway for institutions and groups of similar IVCTs may help ease the prohibitive burdens of premarket review for many developers, including academic medical centers and not-for-profit laboratories. However, we are deeply concerned that FDA once again proposes a caveat singling out transplant and HIV tests as ineligible for precertification, as well as "first-of-a-kind" IVCTs. These blanket prohibitions would disproportionally affect diagnostics for infectious diseases that have long been safely and effectively used to improve patient outcomes while ignoring other areas of medicine where high-risk LDTs have documented concerns.

Further, these caveats are without scientific justification and delegitimize the risk-based core of the FDA proposal by banning arbitrary categories of tests without reviewing validation data. Removing the precertification option for transplant-associated virus viral load testing – an area where LDTs for infectious diseases are most needed – would have devastating effects on patient care that would ripple out to various other areas of medicine affected by transplant ID. If these tests fall out of the precertification category, even large reference laboratories will not be able to keep pace with demand. Additionally, there is no evidence that commercial tests for these viruses (where they exist) are better or safer than tests designed in clinical laboratories.

Similarly, we strongly urge reconsideration of the FDA provision that first-of-a-kind tests should also be exempt from a precertification pathway to permit innovation in the areas of greatest unmet medical need. **If a risk-based regulatory framework is ultimately defined, and a test can display sufficient evidence of validity under its parameters, creating exclusions based on arbitrary categorical designations opposes the principle of a risk-based paradigm and undermines an evidence-based approach.**

Sec. 587G. Advisory committees and Sec. 587T. Communities for IVCTs

Our society appreciates that the FDA TA requests the input of scientific and academic experts, health care professionals, and patient advocacy groups on regulatory and risk-based considerations for IVCTs. As a major stakeholder, IDSA should be included in advisory panels that will be set up to determine risk classifications and provide recommendations on the development and regulation of IVCTs.

Sec. 587W. User fees

We urge Congress to clarify any proposed fees and fee structures accompanying IVD regulation and strongly recommend that an economic impact analysis of high-risk premarket applications be performed as legislation is being considered. This analysis should also take into account the cost of experiments to demonstrate clinical performance as well as an estimate of pre-submission and postmarket institutional review costs. This will be a critical component to assessing the financial feasibility for clinical laboratories to comply with the proposed regulation.

We remain deeply concerned that if clinical microbiology laboratories are required to pay user fees during submission of new tests, this will add another severe burden that will hinder the development of new LDTs and thus patient access to testing. Moreover, these higher costs of testing would likely be passed on to patients, increasing healthcare costs.

IDSA therefore strongly urges any LDT legislation to consider exempting academic and hospital-based microbiology laboratories and public health laboratories from any FDA user fees.

Conclusions

The FDA technical assistance document proposes a regulatory paradigm for *in vitro* diagnostics that departs significantly from DAIA. If enacted, prohibitive requirements for academic and hospital-based laboratories will severely impact public health and devastate ID patient care, particularly transplant medicine. As currently drafted, it is neither a consensus document nor does it reflect the viewpoints of physicians or take current stakeholder discussions into account. It appears to give priority to market-based incentives for commercial test manufacturers and the largest reference laboratories over a goal of providing optimal patient care. Lastly, it champions an overly burdensome regulatory framework.

The current FDA proposal offers multiple costly and time-consuming regulatory structures with no consideration of funding, agency capacity, appeals, or user fees/estimated application costs to developers. **These gaps must be comprehensively addressed. We urge Congress to solicit diverse expert feedback from ID physicians and clinical laboratories across the stakeholder community before introducing any legislation.**

In summary, both ID LDTs and commercial tests play important roles in the care of patients with infectious diseases. 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. We appreciate Congress' ongoing commitment to patient care and public health and your willingness to engage with stakeholders on this complex issue. We hope there will be additional opportunities to provide expertise and work together to craft appropriate policies that spur innovation while protecting 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 or 703-299-1216.

Sincerely,

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