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Food and Drug Administration
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5630 Fishers Lane, Room 1061
Rockville, MD 20852

To Whom It May Concern:

On behalf of the Infectious Diseases Society of America (IDSAs), thank you for the opportunity to comment on FDA's proposed rule on laboratory-developed tests (LDTs).

IDSAs represents over 12,000 infectious diseases (ID) physicians, scientists and other public health and health care providers specializing in the prevention, diagnosis and treatment of infectious diseases. ID physicians rely upon LDTs and commercial tests, typically used in combination with comprehensive clinical assessments, for expeditious diagnosis and management of infectious diseases in complex patients. We share the agency's interest in ensuring the accuracy of medical tests so that ID physicians can make important clinical decisions with the best possible information. Equally important, we are committed to maintaining patient access to critical diagnostic testing. We are deeply concerned that the proposed rule will dramatically curtail patient access to testing, with devastating outcomes for patients with serious infections. We offer an alternative approach that we believe will more effectively meet both FDA goals and patient needs.

IDSAs Recommends Data Collection Prior to Implementing New Regulations

To ensure that a new regulatory framework will achieve the goals of FDA, it is critical to ascertain the complete scope of LDT use and how LDTs lead to both potential benefits and harms for patients. Therefore, **IDSAs urges FDA to delay LDT requirements associated with 510(k) premarket notification or premarket approval, quality system regulation and labeling** until more complete data on LDTs are compiled and made publicly available.

IDSAs supports FDA's proposal to phase out its enforcement discretion for registration and listing requirements and medical device reporting (i.e., severe adverse event reporting) for LDTs and urges FDA to ensure registration, listing and reporting requirements are streamlined and do not pose undue burden on laboratories.

Registration and listing requirements should not include FDA review of an LDT, nor should they impede the use of an LDT.

This approach will provide comprehensive data regarding the full scope of LDTs currently in use and their positive and negative impacts on patient care and public health. These data in turn will allow FDA, in conjunction with the public, to better determine what regulatory framework is most appropriate for LDTs based on actual risk.

Currently we do not have a full understanding of LDTs used in health care practice in the U.S. or the similarities and differences between LDTs used in hospital and health system

laboratories (many of which are nonprofit entities) and those produced by commercial laboratories. FDA asserts in its proposed rule, “Many LDTs are manufactured by laboratory corporations that market the tests nationwide, as they accept specimens from patients across the country and run their LDTs in very large volumes in a single laboratory.”¹ However, many hospitals and health systems produce LDTs for internal use and rely on these tests to inform diagnosis and clinical management of their own patients. A significant number of hospitals and health systems provide diagnostic capacity to smaller, often rural, hospitals in their region. Hospital and health system laboratories have key differences from large commercial laboratories. We agree with FDA that “until FDA systematically collects information on these tests, such as adverse event reports, it will not be able to assess more fully the extent of the risks to patients in the manner it does for other devices.”² More extensive study and data collection are necessary to understand the landscape of LDTs before drafting and implementing a new regulatory framework.

Further, IDSA asserts that if FDA ends enforcement discretion for LDTs, a risk-based approach to regulation should be developed using comprehensive data (to be gathered) on the existing use of LDTs, including any associated adverse events. Limiting regulation to the highest risk LDTs, such as those that would be categorized as Class III, would help limit undue burden on both laboratories and FDA, target resources appropriately and protect the ability of laboratories to offer essential, high-quality ID testing using LDTs with minimal risk. Most ID LDTs should be considered low or moderate risk, as they are typically used as only one part of a comprehensive patient evaluation and not as a singular factor in clinical decision making.

LDTs Are Essential to Diagnosis and Treatment of Infectious Diseases

For many infectious diseases, LDTs are the only – or the most reliable – tests available to provide timely results, especially if the alternative is sending specimens to an external reference laboratory for testing. Many ID LDTs are considered the standard of care, with years of clinical experience, peer-reviewed literature and clinical guidelines supporting their safety, efficacy and use. There is no evidence that the vast majority of ID LDTs are harmful to patients. In the proposed rule, FDA cites specific examples of faulty COVID tests. However, COVID-19 tests were developed for a novel pathogen in response to an unprecedented global public health emergency and should not be considered emblematic of all ID tests.

Our members have reported that if implemented as written, the proposed rule would cause most hospital and health system laboratories to stop offering and developing LDTs because they lack the infrastructure, personnel and financial resources to meet the rule’s requirements. Furthermore, due to the relative infrequency of testing for some critical infectious diseases, reference laboratories may also stop performing these tests as submission of these for clearance by FDA may not be fiscally viable. This would have widespread negative impact on patient care. For ID testing, delays of even a few hours can

¹ Food and Drug Administration, Proposed Rule, Medical Devices; Laboratory Developed Tests Retrieved Nov. 27, 2023, from <https://www.federalregister.gov/documents/2023/10/03/2023-21662/medical-devices-laboratory-developed-tests>.

² Ibid.

be devastating to patients and public health because of missed and delayed diagnoses, given the rapid pace at which some infections can progress to sepsis and/or death – a phenomenon not typically seen with noncommunicable diseases or cancer and genetic diagnostics.

Without LDTs accessible in hospitals and health systems, there would also be dire implications for preventing disease transmission and protecting the public from ID outbreaks. Tests that need to be outsourced would likely be shipped to reference laboratories, which, at full capacity, invariably results in longer turnaround times, especially if they experience markedly increased test volumes as hospital laboratories discontinue performing LDTs. Many infectious diseases can result in fatal or irreversibly debilitating outcomes without proper diagnosis, and LDTs have been developed quickly to help combat emerging outbreaks and support state reference laboratories by providing decreased test turnaround time.

In addition, the regulatory framework laid out in the proposed rule may have the effect of quelling innovation and diagnostic progress that is necessary to keep up with emerging and evolving pathogens. In many instances, including the 2022 mpox outbreak, LDTs have been the first available tests for an emerging infectious disease and have been central to outbreak responses. For commercial test developers, low-volume ID tests that require validation against multiple (and often rare) specimen types are likely to be too expensive to develop and not sufficiently profitable, leaving gaps that are filled by LDTs developed by hospitals and health systems.

FDA asserts that the oversight outlined in the proposed rule may help to advance health equity. However, patients in rural areas will be impacted by the rule more than those in many urban or suburban areas due to workforce shortages, logistical challenges and delays in sending samples to reference laboratories for identification.³ Moreover, as many infectious diseases already disproportionately impact communities of color, low-income people and other vulnerable populations, limiting access to testing will worsen these disparities and decrease diagnostic equity.^{4, 5}

Current Extensive Oversight of ID LDTs Is Effective

Laboratory-developed tests are procedures intrinsic to medical practice. LDTs have been used for decades to diagnose and manage a variety of infectious diseases, and ID physicians have acquired a great deal of experience using these tests to inform diagnosis and treatment of patients. LDTs are well designed and rigorously validated for reliable use in patient care.

³ Deanna Marie Giraldi, Edna Garcia, Iman Kundu, Rex F Famitangco, Disparities in Rural Health Care: A Look at the Field of Laboratory Medicine, *Critical Values*, Volume 11, Issue 4, October 2018, Pages 40–45, Retrieved Nov. 27, 2023, from <https://doi.org/10.1093/crival/vay035>.

⁴ McQuiston JH, Braden CR, Bowen MD, et al. The CDC Domestic Mpox Response — United States, 2022–2023. *MMWR Morb Mortal Wkly Rep* 2023;72:547–552. Retrieved Nov. 27, 2023, from <http://dx.doi.org/10.15585/mmwr.mm7220a2>.

⁵ CDC. HIV and African American People: HIV Diagnoses. Retrieved Nov. 27, 2023, from <https://www.cdc.gov/hiv/group/raciaethnic/africanamericans/diagnoses.html>.

Significant analytical and clinical validity studies support their use. In many instances, ID LDTs have become the diagnostic standard of care and are included in many clinical guidelines.

Current accreditation requirements of the Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists (CAP) provide sufficient oversight for the vast majority of ID LDTs. These tests are developed, validated and implemented by individual laboratories that are CLIA-certified for high complexity testing; testing is performed only at the originating laboratory. Contrary to FDA assertions, clinical validity is assessed for each LDT by laboratories, and is a requirement of CAP accreditation. Often, LDTs are clinically validated in the same way in vitro diagnostic products (IVDs) are validated, in the same laboratories that perform testing for clinical trials aimed at data generation for FDA. Additionally, many of these tests are developed because there is a void in the market for tests for conditions that are of low prevalence, complicating development of a profitable diagnostic product.

Specific Questions Raised in the Proposed Rule

Is there a public health rationale to have a longer phaseout period for IVDs offered as LDTs by laboratories with annual receipts below a certain threshold (e.g., \$150,000)?

A longer phaseout period for LDTs in smaller laboratories would not help alleviate the anticipated harms to patient care. A recent survey of clinical microbiologists highlighted that clinical microbiology laboratories rely heavily on LDTs for improving patient care. Over 90% of labs, including academic medical centers, community hospitals, reference laboratories, public health laboratories and consolidated laboratories, use LDTs, and over 80% have noted that they would consider discontinuing most LDTs if this proposed rule is implemented. A longer phaseout period for labs with lower annual receipts would not help with this issue but would simply delay the inevitable result due to lack of workforce capacity and infrastructure.

If FDA should have a different policy for AMC laboratories, what would be the public health rationale to support such a policy? If FDA should have a different policy for AMC laboratories, is there evidence to support such a policy?

IDSA is concerned about the difficulty in adequately defining an academic medical center (AMC). The definition included in the proposed rule is unworkable. The proposed rule refers to AMCs with “a medical residency training program or fellowship program related to test development, application and interpretation.” This definition does not reflect the reality of medical training because residencies are not connected with test development, application and interpretation; they are connected with patient care. In addition, the requirement for the lab and patient care to be located in the same physical location does not recognize that in many cases, laboratories are sited in a different part of the medical campus than patient-care-related activities. However, if changes are made to these sections of the proposed rule, there may be benefits to some AMC laboratories.

Creating a different policy for AMCs would potentially establish a multitiered system of access to testing that varies depending on the type of facility that a given patient is able to access. This could exacerbate disparities in ID diagnosis and treatment and thus negatively impact patient care. Importantly, many labs that serve major hospitals and/or health

systems are not located in academic settings but nonetheless develop and use ID LDTs that are critical to timely patient care.

Examples of Essential ID LDTs

LDTs are used in a wide array of ID practice areas, including testing for organism identification, antimicrobial susceptibility, HIV and hepatitis virus drug resistance, and tick-borne diseases like Lyme and Ehrlichia. The following ID LDTs have few or no adequate commercially available alternatives, and thus ***this testing is likely to become unavailable if FDA subjects these tests to the full scope of medical device requirements.***

Organism identification: The MALDI-TOF microbial identification databases validated and used by laboratories can identify a much broader range of clinically important organisms than the FDA-cleared databases. The reference method for organism identification is DNA sequencing, yet no FDA-cleared sequencing assay or database exists, so LDTs are routinely used. The ability to identify an organism causing an infection is foundational to the diagnosis and optimal treatment of many infections.

Antimicrobial susceptibility testing: Susceptibility testing panels for bacteria, fungi, *Nocardia* and mycobacteria are mostly LDTs, as the few FDA-cleared panels have substantial limitations, including excluded organisms and an inability to perform off-label testing according to current FDA regulations. There is lack of FDA clearance for less common pathogens, and indeed no regulatory pathway for testing antibiotics that have no FDA-recognized breakpoints. This challenge is substantial – as an example, 19 of the 20 CDC antimicrobial resistance threats are defined by, or treated with, antibiotics for which no FDA breakpoints exist (including *Candida auris*, drug-resistant *N. gonorrhoeae*, drug-resistant *M. tuberculosis* and more). Without a breakpoint, it is impossible to get FDA clearance for a test. Loss of susceptibility testing using LDTs will severely hamper antimicrobial stewardship, greatly increasing the risk that patients will not receive appropriate treatment and potentially accelerating the development of antimicrobial resistance, which is already rising at an alarming rate.

Tuberculosis (TB): LDTs are used to test for resistance to TB drugs, which is critical given increasing rates of resistant TB. Some LDTs have modified FDA-cleared tests to enable testing of additional specimen types, including body fluids and tissues. This approach has been demonstrated to improve patient outcomes.⁶

Non-tuberculous mycobacterial infections: LDTs are the only option for the direct detection of this group of pathogens in patient samples and for antimicrobial susceptibility testing.

Fungal infections: LDTs are state of the art and essential in the diagnosis of serious fungal infections (e.g., those due to *Aspergillus*, *Mucorales*, *Pneumocystis*, *Microsporidium* and

⁶ Buckwalter SP, Connelly BJ, Louison LK, Kolesch JM, Herring SA, Woodliff ED, Bolster LaSalle CM, Gryz TE, Deml SM, Wohlfiel SL, Steinmetz LK, Wengenack NL. Description, validation, and review of a decade of experience with a laboratory-developed PCR test for detection of *Mycobacterium tuberculosis* complex in pulmonary and extrapulmonary specimens. *J Clin Tuberc Other Mycobact Dis.* 2022 Nov 12;29:100340. Retrieved Nov. 28, 2023, from <https://pubmed.ncbi.nlm.nih.gov/36425907/>. PMID: 36425907; PMCID: PMC9679726.

others) that impact immunocompromised (e.g., transplant, cancer) patients. LDTs for these fungal infections are more rapid and sensitive than and are often used in combination with other testing methods for these difficult-to-diagnose infections.

Cytomegalovirus (CMV): LDTs have modified FDA-cleared tests to include additional specimen types required to diagnose CMV infection, the most important infectious complication of organ transplantation. Infants born with congenital CMV are at increased risk for hearing loss, and as such, saliva/oral swab samples are used to test infants who fail hearing screening for CMV infection; notably, this testing is mandated by several states.

Respiratory virus infection: LDTs have modified FDA-cleared tests to include additional sample types, including lower respiratory tract samples, which are important for diagnosis in patients with pneumonia and patients undergoing bronchoscopy to diagnose or exclude lung cancer and other lung conditions.

HIV and viral hepatitis: There are no FDA-cleared tests to detect antiviral drug resistance in hepatitis C virus or hepatitis B virus, and only one such test for HIV. LDTs are routinely used to ensure that individuals with viral hepatitis or HIV are prescribed effective therapy. Loss of these LDTs would likely hamper access to effective treatment for these individuals, worsening their own health and increasing the risk of their spreading infection.

Sexually transmitted infections (STIs): LDTs have modified an FDA-cleared test for chlamydia and gonorrhea to include additional important sample types (which are particularly important for diagnosis in LGBTQ individuals) and samples from children under the age of 14, which have been essential for investigating cases of sexual abuse. This testing is particularly critical given recent increases in STI incidence, including drug-resistant *N. gonorrhoeae*.

Mpox: LDTs were the first available PCR tests for mpox and were critical to scaling up testing capacity. Maintaining the ability to develop LDTs is central to outbreak preparedness and response.

Tick-borne diseases: No FDA-cleared tests exist for the rapid detection of tick-borne pathogens such as *B. burgdorferi* (Lyme disease), *Anaplasma*, *Ehrlichia* and relapsing fever due to *Borrelia* bacteria, despite multiple requests to IVD manufacturers to prioritize these tests.

Thank you for your consideration of our feedback on the proposed rule for laboratory-developed tests. IDSA stands ready to work with FDA to ensure continued access to ID testing. Should you have any questions, please contact Eli Briggs, IDSA director of public policy, at ebriggs@idsociety.org.

Sincerely,



Steven K. Schmitt, MD, FIDSA, FACP
President