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Maintaining Life-saving Testing for Patients With Infectious Diseases: Infectious Diseases Society of America, American Society for Microbiology, and Pan American Society for Clinical Virology Recommendations on the Regulation of Laboratory-developed Tests

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In 2014, the US Food and Drug Administration (FDA) proposed to regulate laboratory-developed tests (LDTs)—diagnostics designed, manufactured, and used within a single laboratory. The Infectious Diseases Society of America, the American Society for Microbiology, and the Pan American Society for Clinical Virology recognize that the FDA is committed to protecting patients. However, our societies are concerned that the proposed regulations will limit access to testing and negatively impact infectious diseases (ID) LDTs. In this joint commentary, our societies discuss why LDTs are critical for ID patient care, hospital infection control, and public health responses. We also highlight how the FDA's proposed regulation of LDTs could impair patient access to life-saving tests and stifle innovation in ID diagnostics. Finally, our societies make specific recommendations for the FDA's consideration to reduce the burden of the proposed new rules on clinical laboratories and protect patients' access to state-of-the art, quality LDTs.

Keywords. laboratory-developed tests; LDT; FDA; infectious diseases; diagnostics.

In October 2014, the US Food and Drug Administration (FDA) released draft guidance proposing to regulate laboratory-developed tests (LDTs). The FDA proposes a risk-based approach, where first high-risk and then moderate-risk test oversight is phased in over a 9-year period. The FDA proposes 3 regulatory oversight exemptions: tests for rare diseases (defined as <4000 tests performed annually nationwide), tests for unmet clinical needs (where there is no FDA-cleared or -approved test), and finally tests for "traditional" LDTs that satisfy the FDA guidance definition (The FDA defines LDTs as an "in vitro diagnostic that is intended for clinical use and is designed, manufactured, and used within a single laboratory") of an LDT.

The Infectious Diseases Society of America (IDSA), the American Society for Microbiology (ASM), and the Pan American Society for Clinical Virology (PASCV) recognize that the FDA is committed to protecting patient safety. The proposed regulations, developed primarily out of concerns over oncology and genetic testing, will have wide-reaching impact on all clinical laboratories. Our societies are concerned that infectious diseases (ID) LDTs, which have little evidence of providing unreliable results that lead to harmful patient care decisions, are not being appropriately considered by the FDA's proposed regulations. Many ID LDTs have a long history of safe and effective use in patient care, and our societies firmly believe the risks posed by ID LDTs are dwarfed by their advances and benefits to patient care. IDSA, ASM, and PASCV submitted comments to the FDA's draft guidance in early 2015, and an additional point-counterpoint on the draft guidance was published in ASM's *Journal of Clinical Microbiology*. With the expected release of the final guidance this year, our societies would like to once again highlight the unique concerns surrounding ID LDTs, and submit recommendations to minimize disruptions limiting patient access to life-saving testing.

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THE IMPORTANCE OF ID LDTS

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 can negatively impact a patient's outcome. To rapidly administer appropriate treatment for infectious illnesses, physicians rely on laboratories to provide clinically relevant diagnostic test results, from both commercial in vitro diagnostics (IVDs) and LDTs, to not only identify the cause of infection but also guide therapeutic selection. Local 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 LDTs to keep pace with newly emerging diseases. ID diagnostics also help protect the broader public health by alerting health officials of the need to trigger protocols to contain outbreaks and prevent the transmission of ID. Last, these tests are vital for guiding clinicians' stewardship of antimicrobial drugs to limit the development of drug resistance as well as enhance hospital infection prevention efforts.

IDSA, ASM, and PASCV support the need to ensure that LDTs are safe and effective tools for the management of patients. However, our societies remain extremely concerned that the FDA's proposed regulations will create serious barriers that could impede patient access to existing high-quality LDTs and also threaten the innovation needed to keep pace with constantly changing and emerging pathogens. The proposed premarket review requirements for clinical laboratories are identical to IVD manufacturers for the clearance or approval of tests. This will likely create a major, and in many cases, impossible challenge for individual clinical laboratories that are already addressing budgetary restrictions from declining reimbursement. These requirements would be so prohibitive of financial and administrative resources that clinical laboratories would be unable to navigate a moderate-risk submission for even one LDT in use, let alone the significantly higher requirements for a high-risk premarket approval (PMA) submission.

These challenges would likely force laboratories to discontinue developing innovative LDTs and either move toward exclusive use of commercial IVDs or send samples for testing to outside reference laboratories. Both of these alternatives pose considerable disadvantages. For example, commercial IVDs are not yet available for the entire range of testing that are currently covered by LDTs, and additionally, a single vendor may not be able to provide all tests required, forcing a laboratory to make expensive investments in new instruments from multiple companies to maintain its menu of testing. Commercial manufacturers may lag significantly in developing tests for emerging or low-incidence diseases, putting patient safety and public health at risk. Most importantly, sending clinical specimens to reference laboratories for testing will 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 same-day results can significantly improve patient outcomes. It is unlikely this turnaround time can be achieved with outside testing by commercial laboratories. The long-term consequences of LDT regulation could be an anticompetitive environment in which broad LDT test menus that are currently available in many medical centers are offered only by large regional for-profit commercial reference laboratories.

IDSA, ASM, AND PASCV RECOMMENDATIONS

IDSA, ASM, and PASCV again offer specific recommendations to improve the proposed regulatory framework and minimize disruption of local, high-quality, ID testing for patient care.

Ensure the Standards Used to Assess the Clinical Validity of LDTs Are Clear and Streamlined

The FDA's draft proposal would require significant human and financial resources. Clinical laboratories using LDTs would be required to comply with standards designed for IVD manufacturers, including fees for submission, the expense of research and development, and the ability to navigate complex FDA regulations, a task often performed by a manufacturer's regulatory affairs division. It is estimated that a "simple" 510(k) submission for a single test would cost between $2 million and $5 million. Clearly, these costs are prohibitive for clinical laboratories and healthcare institutions that are already economically burdened.

It is critical that the FDA examine how it can increase flexibility of moderate-risk premarket review for LDT clinical validity to better take into account the unique challenges clinical laboratories will face during premarket submission. Our societies recommend that the FDA ensure that clinical validity can be established by many sources, including peer-reviewed literature, clinical guidelines, bench studies, data registries, postmarket data, and clinical trials. We also recommend that the FDA examine data sharing models such as ClinGen, where evidence of clinical validity can be "crowdsourced" from multiple laboratories. Given that evidence may vary in quality, our societies offer to provide expertise and guidance with assessing the quality of these areas of evidence. For example, our societies can coordinate with editors of major journals to identify guidelines on how to assess the clinical validity of peer-reviewed literature.

Currently, the College of American Pathologists (CAP) and the Clinical Laboratory Improvement Amendments (CLIA) regulations require that LDTs are analytically validated. Therefore, if clinical validity is demonstrated by a similar commercial high-risk test, clinical laboratories should not be required to redemonstrate this via costly PMA submission. IDSA, ASM, and PASCV also urge the FDA to allow LDTs that are high risk to be compared analytically to high-risk approved devices as predicates.

LDTs for ID Pathogens Should Have an Appropriate Prioritization and Classification of Risk

A straightforward mechanism to assess and classify risk of LDTs is critical. Our societies recommend that the FDA consider past and present uses of LDTs, recognizing different patterns of use in different disease areas, and noting both the benefits that LDTs contribute to patient care as well as their potential harm. 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.

It is vital this process is completed in a timely fashion and is as least burdensome to clinical laboratories as possible. Given the importance of this process, IDSA, ASM, and PASCV would like to offer its member expertise to serve on the FDA's review panels to develop an approach to classify LDT risk. Furthermore, we would be pleased to help convene experts to poll literature and other sources of information to identify tests that have appropriately established safety and clinical validity. Such a mechanism will help limit duplicative efforts to demonstrate proven clinical utility.

In its regulatory framework, the FDA has prioritized oversight of high-risk LDTs for "certain ID with high-risk intended uses," notably viral load tests for cytomegalovirus and possibly Epstein-Barr virus and BK virus. This decision is a major concern for our societies, given the enormous cost of a PMA submission. These LDTs have been in use for many years by clinical laboratories, with well-documented data demonstrating clinical validity and supporting their use in peer-reviewed literature. In many cases, these LDTs have become standard of care. Our societies are happy to see the FDA is open to holding an expert panel meeting devoted to assessing the evidence of risk for viral load testing of transplant-associated opportunistic viral infections. We urge the FDA to begin this process as soon as possible to ensure that these tests are expeditiously assessed and, upon release of final guidance, to better reflect their moderate risk to patients.

Improve the FDA's Oversight Exemption for Unmet Medical Needs

While our societies applaud an exemption to LDTs for unmet medical needs, we are concerned with the process when a commercial test meeting an unmet need is approved. The 12-month phase-in period where laboratories must submit to the FDA or switch to a commercial test will prove difficult to laboratories, most of which operate on a 12-month capital upgrade cycle. Our societies fear there will be cases where laboratories will not be able to purchase the IVD within 12 months, resulting in a loss of capability to conduct testing for the unmet medical need. To address this shortcoming, our societies propose a 2-year phase-in cycle.

Our societies also urge the FDA to delay oversight of LDTs until several (3 or more) commercial tests are approved. With only one option, laboratories may be forced to purchase expensive equipment that may be used for only a single test. Delaying oversight until several tests are available will give laboratories much-needed flexibility to choose tests that are 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 with IVDs. Delaying enforcement until multiple commercial tests are approved will assist clinical laboratories in addressing these issues.

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. We argue that the need to test these nonintended specimens represents an unmet medical need. For example, the 2010 Centers for Disease Control and Prevention sexually transmitted disease guidelines state that rectal and pharyngeal screening of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* must be performed by nucleic acid amplification testing (NAAT). While commercial NAAT IVDs exist for testing urogenital specimens for these pathogens, there still exists the unmet need for testing rectal or throat specimens. Our societies believe clinical laboratories should be able to perform an analytical evaluation using a NAAT IVD when analyzing these new specimens. We recommend that the ability to test alternative sample types for these pathogens should be the subject of enforcement discretion.

Finally, when manufacturers make improvements to tests, it is extremely important that the process that has been created to speed the clearance of the modified test does not limit access to testing. For example, when adding an emerging pathogen to a multiplexed test or making primer modifications to address changing genetic sequences of pathogens within an assay, 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 or genetic modification of the existing pathogen would make the test available to clinical laboratories in a timely manner. Given how rapidly pathogens emerge and evolve, lack of frequent updates is particularly problematic in the area of ID and a key factor in the need for continued flexibility in this disease area.

Laboratory Responses to Public Health Emergencies Must Not Be Hindered

Public health and sentinel laboratories are critical in developing diagnostics to emerging outbreaks, including enterovirus D68, Ebola virus disease, and Zika virus. It is paramount that LDT oversight does not delay their ability to respond to these emerging disease threats. The FDA has indicated that LDTs to emerging diseases will be reviewed under the Emergency Use Authorization (EUA) process. Our societies are concerned that clinical laboratories may lack the technical, regulatory, and clinical resources to navigate the EUA pathway in a timely fashion. We urge the FDA to consider mechanisms to

streamline the EUA process to account for the limited resources available to clinical laboratories.

The FDA has also indicated that the Emergency Investigational Device Exemption pathway can be used to address public health emergencies that do not rise to the level of an EUA, such as chikungunya virus, novel influenza strains, or multidrug resistant microbial infections. However, the FDA has only used this pathway once before, and while our societies are cautiously supportive, it will be critical to ensure this process does not cause undue delay in clinical laboratory responses to an outbreak. We recommend that the FDA closely assess its effectiveness and consider mechanisms on how it can further streamline the review and approval process during local and regional disease outbreaks.

Expand the Regulatory Definition of Rare Diseases for the Purposes of LDTs

For the purposes of diagnostic tests, FDA currently defines rare diseases as those that are tested for no more than 4000 times each year nationwide. Rare ID present some unique challenges to the FDA's current definition, where encephalitis caused by herpes simplex virus or invasive aspergillosis have symptoms similar to widespread common infections. Therefore, they must be tested for at far higher rates than the FDA limit of 4000 per year nationwide. The Center for Drug Evaluation and Research at the FDA defines rare diseases, based on the 1983 Orphan Drug Act, as those that affect <200 000 patients nationwide. IDSA, ASM, and PASCV propose that the LDT regulatory framework aligns with this definition, does not constrain its definition to a pathogen but rather to a disease, and therefore permits continued enforcement discretion for LDTs for rare diseases.

Modify the Definition of a Healthcare System to Better Reflect Real-World Testing

While IDSA, ASM, and PASCV applaud the FDA's carve-outs for oversight exemptions, we are concerned that the restrictions that preclude the testing of patients being treated at a healthcare facility outside of the laboratory's healthcare system will adversely impact ID patient care. In many areas, a large institution's clinical laboratory may serve as a regional reference laboratory to hospitals outside of its system, providing not only a quick turnaround time for tests, but also consultations to discuss laboratory results to ensure that appropriate clinical care decisions are made. The FDA's current definition of a healthcare system precludes oversight exemption for this use of LDTs. We urge the FDA to modify the definition of healthcare system to include instances where local, but nonsystem, healthcare institutions interact to provide diagnostic testing and expertise.

CONCLUSIONS

Both LDTs and commercial tests play important roles in the care of patients with ID, and IDSA, ASM, and PASCV reiterate that economic incentives and appropriate regulation for both types of diagnostics are needed to ensure that patients, and their physicians, have access to cutting-edge quality enhancements in patient care. While we understand that high-risk LDTs would likely require FDA oversight, we strongly urge the FDA to consider exempting FDA review of moderate-risk tests, and instead rely on third-party review by established entities (eg, CAP or CLIA). We also offer the expertise of our members to assist the FDA in developing an equitable oversight of LDTs. Our societies hope that the final FDA oversight activities will facilitate the ever-changing needs of timely ID test development.

Note

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