

December 4, 2023

The Honorable Robert Califf
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Response to Docket No. FDA-2023-N-2177: Proposed Rule on Medical Devices; Laboratory Developed Tests

Dear Commissioner Califf:

The American Society for Microbiology (ASM)--one of the oldest and largest single life science societies with 36,000 members in the United States and around the world whose mission is to promote and advance the microbial sciences--writes to express our serious concerns about the impact on infectious disease (ID) testing of the Proposed Rule on Medical Devices; Laboratory Developed Tests [Docket No. FDA-2023-N-2177]. ASM members perform testing for the diagnosis of infectious diseases in clinical, commercial and public health laboratories in a range of urban and rural settings; including, but not limited to, academic and university-based medical centers, large healthcare systems, private and public community hospitals, independent laboratories, and public health departments. A fall 2023 survey of ASM members reaffirms that LDTs are widely used in clinical and public health laboratories for the diagnosis and monitoring of myriad infectious diseases, underscoring that the proposed changes will have far-reaching implications for public health, for patients, and for the clinicians and laboratories that serve them.¹

We share the FDA's goal of protecting public health by ensuring the safety and accuracy of laboratory developed tests (LDTs) and health equity. **ASM opposes the proposed rule because if finalized and implemented in its current form, we believe many infectious disease LDTs will cease to be offered because the vast majority of laboratories will not have the financial and human resources to submit for FDA approval through either the PMA or the 510(k) pathways.** Laboratories are already operating on a thin financial margin and are facing severe staffing shortages.² Staffing vacancies as high as 25% have been reported with the average vacancy rate ~8.5% and with rural areas particularly impacted.³ The consequence will be the opposite effect of what the FDA intends and instead, patient access to high quality and timely ID testing will be reduced, health inequities will be increased by disproportionately affecting underserved and vulnerable populations, and the innovation that LDTs provide in infectious disease testing will be stifled. The medical device pathway is ill-suited for LDTs focusing on infectious

¹ See survey results in Supporting Information 1-5.

² <https://pubmed.ncbi.nlm.nih.gov/35658527/>

³ [American Society for Clinical Pathology 2022 Vacancy Survey of medical laboratories in the United States | American Journal of Clinical Pathology | Oxford Academic \(oup.com\)](#)

diseases because it does not provide the necessary flexibility and accompanying risk-based framework to meet the real world needs of ID testing and patient care.

ASM Supports a Data Driven Approach Through Registration and Reporting

ASM recognizes that there is a lack of information on the current LDTs on the market. ASM supports registration and listing requirements and severe adverse event reporting for LDTs as a first step toward collecting necessary data and developing a regulatory path for LDTs that is consistent with the realities of how these tests are used in infectious disease care.

Instead, the proposed rule moves forward with regulations without a complete picture of ID LDTs and how they are used in patient care and clinical practice. It raises concerns primarily through anecdotes about errors related to ID LDTs. We agree that more complete data regarding the actual incidence of inaccurate results/patient harm with LDTs as compared to FDA approved assays should be compiled and made publicly available.

Accredited clinical laboratories have quality reporting metrics in place as part of the laboratory and hospital-based quality systems, making LDT severe adverse event reporting feasible. We urge FDA to ensure registration, listing and reporting requirements are streamlined and do not deplete the limited human and financial resources of clinical microbiology and public health laboratories, which do not have dedicated regulatory staff and do not have the funding to hire new staff for these tasks.

ASM Supports a Risk-based Framework

A “low risk” category with enforcement discretion will allow clinical microbiology laboratories to continue with most ID LDTs to serve the most vulnerable communities as well as serve as sentinel laboratories to local and state public health entities in public health emergencies. After collecting data and attaining a more accurate and comprehensive picture of the LDT landscape, ASM believes the FDA in conjunction with stakeholders and the public will be better able to determine a more effective approach to regulation of these tests than the one outlined in this proposed rule. With knowledge of the universe of LDTs and their applications, as well as more robust adverse event reporting, we believe a risk-based approach that maintains enforcement discretion for low-risk tests will be feasible.

Clinicians rely on commercial tests and LDTs, typically used in combination with comprehensive clinical assessments, to diagnose many infectious diseases and support the management of complex patients. Infectious disease test results are not viewed in a vacuum and instead are used as pieces of a puzzle (e.g., traditional bacterial culture, antigen testing, and molecular testing may be ordered together). This allows information to be compared and conclusions to be drawn based on the whole picture. This fact also lowers the inherent risk associated with ID testing, supporting a framework that could allow for continued enforcement discretion.

Below we provide additional information supporting the concerns and consequences of the proposed rule stated at the outset of our comments above.

User Fees are Untenable for Most Clinical and All Public Health Laboratories

The user fee program, designed for commercial devices to fund the FDA personnel needed to enforce the rule and conduct the reviews, is inappropriate and unprecedented for clinical microbiology and

public health laboratories. Many laboratories are not-for-profit and therefore cannot be classified as “small businesses,” and few meet the proposed criteria of less than \$150,000 in annual revenue to allow an exemption as proposed in the rule. Instituting a user-fee program for LDT review as part of the device pathway ignores the enormous difference between commercial device manufacturers and clinical and public health laboratories that develop LDTs. The latter often operate on a thin financial margin within health care facilities without access to the financial and personnel resources available to commercial test developers. It is unreasonable to include these laboratories in the same business category as commercial entities because clinical and public health laboratories are not manufacturers. Many ID LDTs are often developed to address a clinical need at the local level and are not packaged and distributed like commercial IVDs. Applying the funding mechanism associated with the medical device pathway to clinical microbiology and public health laboratories will lead to these entities reducing or ceasing LDT use altogether, the result will be reduced patient access to timely, accurate and reliable tests.

Innovation in Infectious Disease Test Development Will Suffer

LDTs have been at the forefront of clinical innovation in the detection and management of infectious diseases, often leading to their incorporation into guidelines and CDC recommendations. In many instances, including the 2022 mpox outbreak, LDTs are the first available tests for an emerging infectious disease and are central to outbreak responses. According to the ASM survey, 42% of laboratories reported performing >10 LDTs.⁴ The investment in personnel, time and resources required to obtain FDA approval for existing LDTs will halt the development of novel diagnostics, hindering the innovation and diagnostic progress necessary to keep up with emerging and evolving pathogens.

In an era of rising incidence of vaccine preventable diseases and climate change driving spread of pathogens beyond their traditional endemic areas, clinical microbiology laboratories serve as sentinel laboratories for the public health network and will likely be the first point of contact for emerging diseases. The FDA LDT proposal will limit the ability of these laboratories to respond to local needs in a timely manner. In addition, the challenges the medical device approval pathway will present to clinical laboratories running LDTs will lead to loss of expertise in performance of these tests over time. This will degrade our ability to identify and respond to future pandemics and novel pathogens.

Patient Access to High Quality ID Tests Will Be Compromised, Furthering Health Inequity

Clinical laboratories often validate and implement LDTs because there are diagnostic gaps and clinical needs for rapidly and accurately diagnosing an array of critical pathogens.⁵ The existing diagnostic gaps currently filled by LDTs highlight the discrepancy between essential patient needs and priorities of manufacturers. Although the number of commercially available IVD products for infectious diseases has increased in the last couple of decades, gaps will remain because the commercial market provides inadequate incentive for manufacturers. Simply put, the investment to develop, manufacture and gain approval must be worth the anticipated profit for the companies. For laboratories, these tests are required for patient care and guided by professional society clinical practice recommendations, which is a moral imperative over financial viability. The pathway proposed in the rule offers no approaches or strategies to address this reality. Compounding this problem is the fact that the proposed rule and

⁴ See survey results in Supporting Information #3

⁵ See survey results in Supporting Information #4, #6, and #7

medical device pathway offer no exemptions for LDTs that address unmet need, humanitarian uses or public health indication beyond surveillance.

Difficult decisions will need to be made that pit financial cost against the cost of not having critical diagnostics for patient care. These tests are often neither high volume nor profitable, making a costly regulatory process for approval untenable for laboratories. Some of the patient populations for which LDTs are the only option are among our most vulnerable, as many infectious diseases disproportionately impact historically underserved racial and ethnic communities, low-income individuals and those living in rural areas, those who are uninsured, and even pediatric and immunocompromised patients. Limiting access to testing will worsen existing health disparities and inequities.

For public health laboratories, antibody testing, serotyping of viruses and bacteria are other unmet needs for infectious diseases with significant diagnostic and public health implications but few FDA approved assays. These assays are LDTs because demand is not high enough to warrant interest from manufacturers. For example, measles and varicella zoster strain typing is important for differentiating between wild type virus and vaccine derived virus, which have different public health and clinical management implications. Serotyping is also used for tracing outbreaks as well as treatment decisions, for example the detection of *Salmonella enterica* serotype typhi versus non-typhoidal serotypes. The use of next generation sequencing for the rapid identification of pathogens of public health interest as well as the early detection of novel resistance mechanisms will also be affected by the proposal.

Single target infectious disease LDTs are at risk under the proposed rule, but they provide necessary, affordable care for patients. Some tests for pathogens are only available as part of a large FDA approved panel with no single target FDA cleared assays.⁶ The result is unnecessary panel testing, which also results in insurance coverage denials. Patients are being handed large out-of-pocket expenses and therefore testing for specific pathogens is not financially feasible for patients.

Certain regional diseases rely heavily on LDTs to protect public health, with their populations often representing the most vulnerable and underserved. Arizona and New Mexico have some of the largest Indigenous American populations, mostly located in remote rural settings. These areas experience endemic infectious diseases like Hantavirus and Coccidiomycosis, which can be fatal and require rapid diagnosis. Neither of these infections have FDA approved molecular nor antigen assays available and these infections occur infrequently in the general population, providing no incentive for manufacturers to undergo FDA approval with little, if any, financial reward. Because rapid diagnosis is important, sending out the sample to a large reference laboratory compromises the timeliness needed to address these infections.

Test Modifications Are Necessary for Comprehensive ID Testing

To offer the most comprehensive testing in ID, test modifications are often necessary to account for the gaps in clinically relevant specimen sources and requirements of FDA approved IVDs. Test modifications under the existing medical device pathway are considered “remanufactured” and therefore may require additional review. The time, financial, and human resources do not exist in clinical and public health laboratories to put modifications back through an approval process without negatively affecting patient

⁶ See survey results in Supporting Information #7

care. Most ID test modifications do not affect analytical or clinical validity or change intended use. It is unclear from the proposal what the threshold of change would be to require resubmission as a “remanufactured” test, and whether it affords the necessary flexibility to best serve patients.

ASM found that 73% of surveyed laboratories currently use modified FDA approved assays to better serve their patient population.⁷ Modifications range from using a chemically equivalent transport media that is not the exact company or product number as indicated in package insert to using a non-approved, but clinically relevant, sample type.

The Proposed Rule Will Delay ID Laboratory Testing When Time is of the Essence

With the rule in place, clinical microbiology laboratories would be forced to send many specimens to external reference laboratories for testing because there will not be human or financial resources available to navigate the premarket approval process. Sending specimens to external reference laboratories takes the testing further from the site of patient care and dramatically increases testing time. Health equity is compromised as communities lose access to local testing and underserved/high risk populations will be disproportionately affected by delayed results and increased turnaround time. Patient care is compromised as delays in turnaround time can be dangerous for a patient with an undiagnosed infectious disease.

Turnaround time is of the essence when diagnosing an infectious disease, especially for infections associated with high mortality and morbidity such as meningitis, encephalitis, and sepsis. Accurate treatment is contingent on rapid diagnosis and antimicrobial susceptibility testing, when appropriate. LDTs are frequently used in both areas and additional barriers to use will further delay results and treatment. Without timely proper identification of a pathogen, an ineffective or otherwise inappropriate antimicrobial may be prescribed for a patient, with the added danger of increasing antimicrobial resistance.

Regulations Must Consider Antimicrobial Susceptibility Testing

We are concerned that the proposed rules offer no exceptions for antimicrobial susceptibility testing. Susceptibility test panels for bacteria, fungi, *Nocardia* and mycobacteria are mostly LDTs, as the few FDA cleared panels have substantial limitations and there is lack of FDA clearance for less common pathogens. There are no FDA breakpoints for susceptibility tests for many of the pathogens listed as CDC urgent and serious antibiotic resistance threats (including *Candida auris*, drug resistant *N. gonorrhoeae*, carbapenem-resistant *Acinetobacter baumannii*, and more). Without a breakpoint, a laboratory would unlikely be able to get FDA clearance for a test that applies non-FDA interpretive breakpoints (CLSI or EUCAST), which creates a “catch-22” situation given the agency’s role in breakpoint approval. Laboratories will have to default to the breakpoints for which the assays received FDA approval, which are also out of sync with many of the CLSI updated breakpoints.

Hindering and potentially losing susceptibility testing in laboratories close to the patient is harmful to patient care. Without this capability, antimicrobial stewardship will be compromised, greatly increasing the risk that patients will not receive appropriate treatment. Beyond the harm this causes the patient, it

⁷ See survey results in Supporting Information #1 & 2

contributes to antimicrobial resistance and affects public health. We urge FDA to consider exceptions or, at a minimum, continued enforcement discretion for antimicrobial susceptibility testing.

Conclusion

ASM agrees that ensuring accuracy of diagnostic tests is essential to patient safety and high-quality patient care. But a regulatory pathway applied to LDTs must be flexible and designed with the clinical realities of how LDTs are widely used in ID testing in mind. As proposed, the regulatory pathway outlined in this rule will have harmful, unintended consequences. This will result in the reduction and in some cases, complete cessation of critical ID LDTs, threatening patient access to high quality, timely ID testing, reducing health equity and eroding our preparedness for the next pandemic.

We appreciate your consideration of our views. If you have questions, you may contact Allen Segal, ASM Chief Strategy and Public Affairs Officer, at asegal@asmusa.org.

Sincerely,

A handwritten signature in black ink, appearing to read "L. P. Samuel", written over a large, hand-drawn triangular shape.

Linoj P. Samuel, PhD, D(ABMM)
Chair, ASM Clinical and Public Health Microbiology Committee

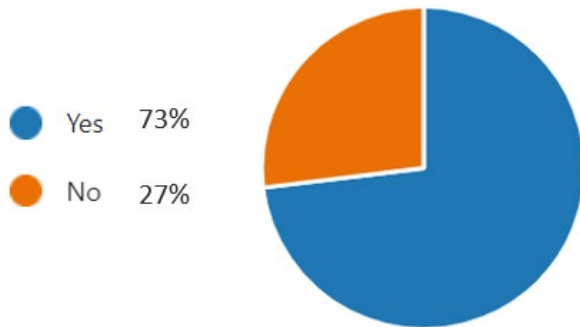
Supporting Information

ASM conducted an online survey that was sent to the ASM members who are directors of clinical and public health microbiology laboratories. This survey had 88 respondents across the United States. Of the respondents, 56% (50/88) represented academic medical laboratories, 6.8% (6/88) represented public health laboratories, 10.2% (9/88) represented community hospital laboratories, 13.6% (12/88) represented reference laboratories, and 12.5% (11/88) represented other types of clinical microbiology laboratories, including those that are consolidated laboratories serving an academic medical center. Data from this survey can be found in S1-S5.

S1. Proportion of ASM Laboratories Utilizing LDTs

LDT Usage	% of Surveyed Laboratories (n=88)
Fully LDT only	19
Modified FDA approved only	7
Both fully LDT and modified FDA approved	64
None	10

S2. Proportion of ASM Laboratories Utilizing LDTs that are Modified FDA Approved Assays (n=88)



S3. Number of LDT Assays Utilized by Surveyed ASM Laboratories

Number of Unique LDT Assays Currently Performed	% of Surveyed Labs (n=88)
1-5	33
6-10	24
>10	42
N/A	1

S4. Rationale for why ASM Member Laboratories Use LDTs

Rationale for Utilizing Current LDTs in their Laboratory	Percentage of Surveyed Laboratories Who Cited This Reason (n=88)
No FDA approved assay for the pathogen	70%
No FDA approved assay for the specimen	74%
No FDA approved assay for the patient population	42%
Limitations of FDA approved assay (transport media requirements, etc.)	49%

Not available on currently used platforms	41%
Target is only available as part of a large panel	25%
Other reason not listed	16%

S5. Surveyed ASM Laboratories that Perform LDTs Plans if Proposed Rule Passes

Plan	% of Laboratories (n=88)
Submit all LDTs for FDA approval	18%
Submit some but not all LDTs for FDA approval	33%
Submit no LDTs for FDA approval and discontinue offering any LDTs	17%
Unsure, but considering discontinuing tests	32%

S6. Examples of pathogens or patient population-specific needs with no commercially available IVD

a. **Fungi:** despite the rapid increase in fungal infections globally, there is no FDA approved molecular assay for the majority of endemic and emerging fungal pathogens, including, but not limited to, *Aspergillus*, *Coccidioides*, *Blastomyces*, *Histoplasma*, *Mucormycosis*, and *Candida auris*. These fungi require rapid diagnosis, treatment, or isolation. Molds have a low recovery rate in fungal culture, leading to misdiagnosis and underdiagnosis, contributing to higher mortality and morbidity.

b. **Travel-related infections:** Vector-borne (e.g., mosquito, tick, etc) pathogens are particularly underrepresented in available diagnostics. *Plasmodium* spp., dengue virus, Chikungunya virus, West Nile virus, *Anaplasma*, *Ehrlichia*, *Babesia*, and *Trypanosoma* do not have FDA approved molecular assays, hindering diagnosis and timely intervention.

c. **Emerging and re-emerging infections:** Measles and mumps do not have FDA approved molecular assays available. Measles is extremely contagious as it is airborne and remains infectious in the air for hours. To contain and prevent further outbreaks, rapid diagnostics are warranted and this currently can only be achieved by LDTs.

d. **Immunocompromised patients:** Immunocompromised patients are at a higher risk for a variety of infections that otherwise rarely or less severely impact immunocompetent individuals. Diagnosis via LDT assays, including CMV viral load on BAL, HHV-6 viral load, adenovirus viral load, and *Pneumocystis jirovecii* PCR are particularly important in this population and have no standalone FDA approved assays available.

e. **Mycobacterium assays:** There is only one FDA approved test currently available for the molecular detection of *Mycobacterium tuberculosis* from a single specimen type and there are currently no FDA approved tests available for the rapid identification of *M. tuberculosis* from positive cultures. Nontuberculosis mycobacteria also lack FDA approved diagnostics and differentiating between species requires lengthy and low yield culture.

f. **Infections in Pediatrics:** There are no FDA approved molecular assays for sexually transmitted infection screening in pediatrics.

g. **Bacterial and fungal identification:** Even with the advent of MALDI-TOF, many species and organisms, spanning bacteria to fungi, are only in the “research use only” (RUO) database, requiring validation as an LDT for clinical use.

S7. Lack of Standalone Target Assays Available

This has occurred with testing for some gastrointestinal (GI) pathogens and viral causes of meningitis/encephalitis. For example, there are no FDA approved standalone PCR assays for many of the GI pathogens including *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium*, and *Cyclospora*. Similarly, there are no standalone FDA approved PCR assays for detecting Enterovirus, Parechovirus, or CMV from cerebrospinal fluid. Additionally, the totality of targets do not always apply based on a patient's risk factors and clinical presentations. In these cases, more limited, targeted testing is clinically indicated.