The Reliability And Accuracy Of Laboratory-Developed Tests

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Abstract

The Food and Drug Administration (FDA) issued a proposed regulation in October 2022 that eliminates the ability to enforce regulations for tests developed in laboratories (LDTs). The FDA's proposal delineates a five-stage approach to implementation to start the regulation of LDTs in a manner similar to that of commercial in vitro diagnostic procedures (IVDs), including amended FDA-approved/cleared tests. This paper presents an overview of topics pertaining to the medical and public health microbiology laboratory. We believe that LDTs conducted by individual diagnostic labs recognized by Clinical Laboratory Improvement Amendments should not be subject to the same regulatory measures as commercial IVDs. If this regulation is implemented, it would have adverse effects on the diagnostic services now provided by clinical and public health labs, thereby affecting patients and their healthcare professionals. The cessation of enforcement discretion is expected to impede diagnostic innovation and diminish the availability of diagnostic testing, hence compromising health fairness. Moreover, the insufficiency of infrastructure, including both human resources and financial resources, within the FDA and diagnostic labs poses a significant hindrance to the necessary submissions for evaluation. Diagnostic labs, similar to the FDA, place a high importance on patient safety, precise clinical diagnosis, and ensuring fairness in healthcare. Given the existing lack of knowledge on the extent of the LDT landscape, we endorse the implementation of a registration procedure and a

straightforward system for reporting adverse events. This will allow us to get a comprehensive understanding of the clinical applications of LDTs and any related safety issues. It is essential that regulatory rules be grounded on methodically collected facts rather than relying on anecdotes or case reports. In the context of infectious disease diagnostics, it is essential for a regulation to effectively reconcile the possible adverse effects on patient care with the practical safety hazards involved.

Keywords: regulation authority, in vitro diagnostics, reliability and validity.

1. Introduction

The regulation of laboratory developed tests (LDTs) is governed by two distinct frameworks. The first framework, known as the Medical Device Amendments, was established over 45 years ago to grant the FDA (Food and Drug Administration) extensive jurisdiction over diagnostic tests. The second framework, referred to as the amendments to the Clinical Laboratory Improvement Act (CLIA) of 1988, is responsible for overseeing laboratory practices. The FDA and the Agency for Medicare and Medicaid Services, or CMS, are responsible for enforcing these two laws. Prior to the publication of the proposed rule on October 3, 2022, the FDA deemed enforcement discretion to be enough for LDTs (1).

Nevertheless, the organization directed its efforts towards the supervision of business testing supplies, which were produced, extensively promoted, and distributed to be utilized across numerous establishments. Meanwhile, the Clinical and Laboratory Improvement Act (CLIA) establishes and enforces laboratory standards for all institutions that conduct health assessments or diagnose, prevent, or cure diseases using human specimens. The Clinical Laboratory Improvement Association (CLIA), a regulatory body overseen by the Centers for Medicare and Medicaid Services (CMS) in collaboration with the Center for Disease Control and Prevention (CDC), sets out performance criteria that pertain to the analytical validity of a given test system within a laboratory setting. The laws set out by the Clinical and Laboratory Improvement Act (CLIA) enforce quality requirements for laboratory testing conducted on human specimens with the aim of diagnosing, preventing, or treating diseases, as well as assessing health. Although CLIA guarantees the precision and dependability of testing, the FDA

is solely responsible for evaluating the clinical reliability of an examination.

The FDA declared its intention, for the initial time, to oversee all LDTs in 2010. This was a result of the FDA's increasing apprehension over the increasing complexity of LDTs, particularly in light of prominent examples such as the OvaSure ovarian cancer test. This test resulted in needless procedures for women who obtained positive results for ovarian tumor blood indicators. In 2014, the government officially announced its intention to regulate LDTs by informing Congress and publishing draft advice. This decision was taken in response to technological and scientific improvements in genetic and biomarker identification across several illness categories. The primary objective of the FDA was to transition the fundamental criterion for these tests from a safety and effectiveness-oriented approach to one that places more emphasis on medical and scientific accuracy. At this juncture, there was a notable surge in Congressional focus on the matter, prompting the House Committee on Energy and Commerce to convene hearings pertaining to the subject matter. Legislative initiatives were initiated by members of Congress with the aim of addressing the issues raised by the FDA and strengthening its regulatory jurisdiction over every type of in vitro diagnostic procedures (IVDs), particularly LDTs.

The 2014 preliminary advice delineated a regulatory structure that would enable the FDA to transition from using enforcement authority to mandating pre-market evaluation of certain tests. The structure under consideration relied on risk assessment, and the instructions provided indicated that LDTs could be classified into three distinct categories: (1) examinations that would be exempted from regulatory oversight (2); tests that would solely necessitate FDA registration as well as notification of adverse events (3); and (3) tests that would necessitate pre-market evaluation and adherence to set quality standards (3). Tests classified as "high risk" must undergo the whole pre-market assessment procedure. Significantly, while the FDA asserted its ability to enforce flexibility power, proponents of Congress, in conjunction with other officials within the agency, advocated for the reinforcement of the FDA's stance via legislative measures. The issue surrounding the FDA's jurisdiction to oversee these tests and the potential alignment of such monitoring with the existing regulation related to clinical laboratory activities under the Clinical and Laboratories

Improvement Act (CLIA) continues to be a subject of contention.

The 2014 draft guideline from the FDA, along with the attention it received from Congress, generated significant controversy among the healthcare and clinical laboratory professions. Some individuals expressed strong opposition to the guidance, arguing that it infringed upon the principles of medicine and regarded labs as producers of medical devices. Conversely, the opposing viewpoint revolves on apprehensions over patient security and the apathy shown by patients towards the specific methodologies used or the location of the test, since their main priority is the attainment of accuracy. There were also concerns raised over the existence of two regulatory pathways, namely manufacturers undergoing pre-market clearance while LDTs do not, which resulted in an imbalanced competitive environment. In 2016, the Food and Drug Administration (FDA) conducted public hearings and received a substantial number of public views about the draft guidelines. However, during the closing weeks of the Obama Administration, a decision was reached to postpone the issuing of any definitive guidance. During the first stages of the Trump Administration in 2017, a deliberate choice was taken to suspend the progress of final guidelines, opting instead to provide sufficient time for an extensive community deliberation and legislative strategy.

The revised legislative strategy aimed to provide a fresh definition and structure for in vitro diagnostics (IVDs) known as "in vitro clinical testing" (IVCTs). This would encompass all assessment programs and diagnostic procedures, notably laboratory diagnostic tests (LDTs). Multiple versions of legislation have been introduced since 2014, but the bipartisan Validating Appropriate and Leading-edge In Vitro Detection (VALID) Act gained the greatest support on Capitol Hill. The measure eventually did not succeed in being passed before the end of 2022, prompting the FDA to initiate its own regulation process.

The suggested rule outlines the FDA's argument for gradually eliminating the authority to enforce LDTs. The agency's rationale is that it no longer considers enforcement discretion to be adequate in guaranteeing the clinical reliability of LDTs and safeguarding patients from erroneous tests that may have detrimental effects on patient well-being. The FDA asserts that LDTs should undergo the same pre-market

clearance procedure as commercially created test kits. Additionally, the agency contends that it is unable to safeguard patients without knowledge of the "universe" of LDTs in use and with no mandatory reporting of adverse events. The complexity and criticality of LDTs in medical fields such as cancer, genetics, and newborn screening have grown significantly. These tests play a crucial role in medical decision-making, which may have life-or-death implications. However, infectious disease testing had not received significant attention until the onset of the COVID-19 pandemic. The rationale for the proposed regulation is based on concerns over the quality of emergency use authorizations obtained for COVID-19 testing during the public health crisis (4).

In addition to worries regarding patient security and medical reliability, the FDA argues that the enforcement authority for LDTs hampers innovation by providing an alternate route and motivation for firms to create more advanced diagnostics. According to the FDA, removing the ability to enforce regulations will help to stabilize the testing market. The organization also asserts that enhanced supervision of LDTs would promote health equality, highlighting apprehensions that erroneous outcomes from LDTs might worsen disparities in marginalized communities.

2. Laboratories Create, Verify, and Execute LDTS.

LDTs are used in medical and public health labs for a multitude of pragmatic purposes. Numerous cases necessitated the use of inventive methodologies to tackle complex clinical situations, including the identification of fungal infections, the detection of viral illnesses in transplant recipients, and the provision of antimicrobial sensitivity data for novel antimicrobial agents. Given the lack of FDA-approved or authorized tests for these specific indications, labs have taken proactive measures to address the requirements of healthcare providers and patients. They have used their knowledge to create, verify, and execute Laboratory Diagnostic Tests (LDTs).

There are still significant deficiencies in the diagnostic tools that have been authorized or certified by the FDA and are accessible to healthcare professionals and labs. Clinical recommendations and the CDC advise the use of molecular techniques to identify Pneumocystis jirovecii in different patient samples. However, there are currently no single-target molecular tests authorized or certified by the FDA for this

disease (5, 6). The identification of Mycobacterium tuberculosis is now confined to a particular specimen type, since there exists just one commercially accessible FDA-approved platform for this purpose. Furthermore, the only DNA probes now accessible for the expeditious detection of M. Positive cultures of TB and other mycobacteria have been removed from the market (7). Numerous fungal illnesses, such as aspergillosis and coccidioidomycosis, lack a substantial number of FDA-approved or certified diagnostics (8).

Despite a major clinical need, there is a lack of FDA-approved or approved antimicrobial resistance screens for yeast, non-tuberculous mycobacteria, or Nocardia (9, 10). Laboratories may verify and apply non-FDA approved/cleared boundaries and/or disk or gradient dispersion screening due to constraints with IVD antimicrobial resistance test methods, such as the absence of antimicrobials contained on an array or efficiency limits.

The existing microbial detection datasets for industrial matrix-assisted laser desporption ionization - duration of flight mass spectrometry (MALDI-TOF MS) do not include all clinically significant species. Consequently, labs have used these systems in an off-label manner by validating new organisms. Furthermore, labs have conducted validations on alternate extraction methods, medium, and colony age in order to enhance the efficiency of MALDI-TOF MS analysis. In cases when organisms cannot be identified using MALDI-TOF MS or other commercially available identification techniques, several labs, including the FDA, employ sequenced as an alternative technique. It is worth noting that there is currently a lack of sequencing identification tests that have been authorized or certified by the FDA.

LDTs have been integrated as an essential element of clinical guidelines and recommendations. These include the assessment of hepatitis B or hepatitis C antiviral resistance, the measurement of HHV-6, adenovirus, or BKV in transplant recipients, the examination of oral and rectal specimens or pediatric patients for infections transmitted through sexual contact, and the screening of non-tuberculous mycobacteria for antimicrobial susceptibility (6, 9, 11 – 16). Historically, the FDA only permitted HIV testing for viral load to monitor medication response, despite the CDC's recommendation to utilize molecular tests for diagnosis (17).

At first, viral load tests for detecting cytomegalovirus were only authorized for some subgroups of transplant patients, while not being allowed for others. Certain assays have subsequently obtained approval or clearance from the FDA. However, their initial acceptance and use as laboratory diagnostic tests (LDTs) prompted the formulation of recommendations that enhanced the quality of patient care. In addition, the utilization of LDTs, such as off-label IVDs, has generated the motivation and market need for diagnostic makers to contemplate allocating the substantial resources necessary to acquire FDA approval/clearance and introduce an examination to the market (for example, test for chlamydia and gonorrhea using oral and rectal swabs).

In some instances, there exists a situation where FDA-approved or authorized tests are only accessible from a single diagnosis company, such as the quantitative viral load measurement for BKV and EBV.

Although the availability of IVD alternatives for these infections is praiseworthy, laboratories may have difficulties in promptly adopting the IVD test. Frequently, this entails substantial financial commitment, and the use of the platform may be difficult to rationalize for a single or many low-volume tests. Anticipating that laboratories would promptly confer a de facto monopoly onto the first diagnostic producer to get FDA approval/clearance might potentially yield harmful outcomes. In contrast to the FDA's claim, the use of LDTs in the majority of medical and community-based microbiology labs does not result in cost savings, but rather necessitates a substantial allocation of limited time and resources for their development and upkeep.

Laboratories are compelled to use the creation of LDTs in order to tackle the significant diagnostic deficiencies mentioned before. The current laboratory accreditation procedure based on the Clinical and Laboratory Improvement Act (CLIA) places a higher level of regulatory scrutiny on LDTs compared to FDA-approved/cleared diagnostics utilized by a comparable laboratory. The verification of such experiments requires a substantial amount of effort, which extends beyond the initial validation phase to include quality control and monitoring. Due of these factors, laboratories typically shift

towards FDA-approved/cleared alternatives wherever possible.

Certain Laboratory Diagnostic Tests (LDTs) are only accessible at national or local laboratory references. The proposed regulation by the FDA is expected to further promote the usage of reference laboratories for testing, perhaps leading to a decrease in the utilization of local testing facilities. The excessive dependence on clinical laboratory testing often fails to adequately meet the requirements of both the individual and the healthcare organization. For instance, there may be diagnostic requirements that are unique to a particular locality and not accessible at a reference laboratory. This might include specialist pediatric testing or the genetic identification of antibiotic resistance in regions with a high frequency of sexually transmitted infections (STIs).

The use of reference laboratory testing is hindered by delays, which contradicts the need for rapid findings in order to enhance patient outcomes (18). The exclusive dependence on reference labs poses significant challenges in establishing a meaningful contact between medical professionals and the laboratory conducting the test. The link between these factors is crucial for accurately interpreting and using any laboratory tests, including LDTs. Moreover, the capacity to create LDTs enables laboratories to cater to the distinct requirements of the local populace, particularly specialized underprivileged communities, which has played a crucial role in combating infectious illnesses. The integration of laboratories with local patient care, enabling the collaborative development of laboratory diagnostic tests (LDTs) with healthcare providers, is not only crucial for delivering optimal clinical care but also plays a pivotal role in enhancing diagnostic methods that have grown into essential components of the standard of care.

3. Summary Of The Proposed Rule For 2022

The FDA's Center for Medical Devices and Radiological Health has filed a proposed rule on October 3, 2022, which aims to modify rules to clearly state that all intravenous devices (IVDs) are considered methods within the Federal Food, Drug, and Cosmetic Act. This includes cases when the "manufacturer" of an IVD is a laboratory. According to the regulation, test systems produced by labs are considered as devices. Furthermore, the proposed regulation aims to gradually eliminate the ability to impose LDTs within the jurisdiction of the device authority.

Consequently, after a period of four years, the majority of LDTs will be required to undergo pre-market assessment.

The process of gradually reducing enforcement discretion would occur in five distinct phases over a period of four years after the publication of a final rule, with a deadline of April 1, 2028. The process commences with a gradual elimination of general enforcement authority for medical device declaring (MDR) demands and modification and elimination reporting requirements after a period of one year. This is followed by the implementation of authorization and further specifications by the conclusion of the second year. Subsequently, enforcement authority for high-risk tests is terminated, with a deadline of October 27, 2027. Finally, enforcement authority for low-risk tests is terminated after a period of four years.

The proposed regulation, in accordance with the medical device power granted to the FDA, adopts a far more rigid stance compared to the approach put forward in the latest version of the VALID Act. The absence of "grandfathering" regulations for LDTs currently available in the market, the lack of broad legal authority for low-risk tests, and the shorter implementation period compared to the legislation (4 years versus 9 years) are notable differences. Additionally, the VALID Act incorporates additional exemptions to pre-market review, such as antimicrobial susceptibility tests and beneficial use, which surpass the proposed rule.

4. The Concerns Raised By Clinical and Health-Related Laboratories

The FDA's portrayal of LDTs as hazardous and detrimental to public health is a matter of concern. The proposed regulation offers several anecdotal instances of hazardous LDTs. With the exception of the COVID-19 EUA guidance, the aforementioned instances do not pertain to testing for infectious diseases. The majority of individuals fail to acknowledge that LDTs are currently subject to regulation by CMS/CLIA and that laboratories already possess established quality procedures. Indeed, the extent of the possible problem remains uncertain.

The precise quantity of LDTs used by clinical labs remains unknown, as is the precise count of serious adverse events particularly linked to LDTs. Similarly, the quantification of the health benefits supplied by LDTs to the general population has not been conducted. For instance, LDTs provide supplementary diagnostic capabilities for infectious diseases

and have the potential to decrease the need for wasteful sample, testing, and treatment. How does the risk-benefit ratio compare to the possible negative impact of excessive regulation? What is the comparative analysis of error rates between LDTs and IVD tests? The assertion that dangerous LDTs pose a significant concern and exhibit mistake rates greater compared to those of IVD examinations lacks scientific basis, since it relies only on anecdotal information rather than methodically gathered data.

The proposed regulation is based on the assumption that LDTs are healthcare products and should be controlled accordingly, despite the lack of a precise definition. LDTs, which are created, verified, and put into practice by individual labs that are accredited by CLIA to conduct complicated testing, are not produced, packaged, or marketed for use. The testing is only conducted in the laboratory where it originated. Laboratory-developed procedures (19) have been more accurately characterized as LDTs. LDTs have been contested by several clinical labs, doctors, and professional and medical bodies on the grounds that they do not meet the criteria of being medical devices as defined by the 1976 Modification to the FD&C Act. Considering that Congress has deliberated on legislation providing the FDA with the power to oversee LDTs (specifically, VALID), it is logical to infer that the FDA now lacks the jurisdiction to govern them as medical equipment.

The proposed regulation lacks a precise definition of the criteria for determining an LDT that requires submission and evaluation by the FDA. The presence of LDTs that deviate from the "1976-like" standard is acknowledged, although the precise definition of out-of-scope LDTs, beyond those involving manual, non-automated procedures, remains ambiguous and open to varying interpretations.

While we acknowledge the notable progress made in diagnostics since 1976, it remains unclear how labs will ascertain the true nature of an LDT. Does this include the process of verifying and evaluating different kinds of specimens or transportation medium for an IVD that has been authorized or cleared by the FDA? Does this include the examination of patients who are not explicitly mentioned in the use guidelines (such as pediatrics, immunocompromised individuals, but not post-transplant recipients)? Is the inclusion of an automated component exempt from microscopic or culture-based methods? Do phenotypic antimicrobial

susceptibility testing or resistance detection techniques fall under the area of investigation? If the concept of an LDT include these situations, it will have a profound influence on diagnostic microbiology, resulting in substantial ramifications for patient treatment.

The proposed regulation is unlikely to stimulate diagnostic innovation, contrary to the FDA's assertion. Without further incentives to address diagnostic gaps, both private producers and autonomous CLIA-certified labs will be hindered in their ability to innovate. As previously said, clinical labs have verified and used LDTs due to a diagnostic void linked to a clinical need. Numerous tests, albeit not universally applicable, exhibit a comparatively small volume. This may be attributed to either the specific conditions whereby a patient might require the diagnostic test (such as severe immunocompromised individuals or those with serology-positive results) or the general prevalence of the illness among the patient population.

Despite the recent growth in the availability of intravenous drug (IVD) treatments for infectious illnesses, commercial manufacturers must nevertheless take into account a certain threshold when making investments in the necessary research and FDA applications required to introduce an innovative IVD to the marketplace. In essence, the expenditure must be commensurate with the expected reward. The commercial development of particular, low-volume tests that need distinct specimen types or are linked to a low frequency infectious illness would incur significant costs. Presently, there is a lack of motivation for corporations to address the diagnostic deficiencies that are presently being met by LDTs in several labs.

Despite the presence of some tests introduced by commercial manufacturers (which we acknowledge as beneficial), the unavailability of LDTs will still result in a substantial delay and adverse effects on patient care. Both commercial innovation and the innovation provided by independent CLIA-certified laboratory settings are expected to be hindered. Owing to the legislative and economic costs, several clinical labs will cease the use of present LDTs and cease the development of LDTs when novel clinical requirements emerge. The capacity of pioneering therapeutic and public health labs to provide laboratory diagnostic tests (LDTs) and disseminate the corresponding clinical efficacy is more inclined

to stimulate commercial innovation compared to excessive regulation of these tests.

In contrary to the assertions made in the proposed regulation, it is our contention that the finalization of the rule would have a detrimental effect on health equality. Clinical labs that are accredited to do high-complexity testing, such as LDTs, provide convenient access to testing services in close proximity to the patient's treatment location. One possible issue associated with the regulation is the possibility of testing being redirected to centralized reference labs. The validity of this assumption is contingent upon the reference labs' capacity to get FDA approval or clearance for LDTs. If nationwide testing is directed towards a limited number of reference labs, there will be a significant increase in the time required to get results. This phenomenon may be comprehended given that reference labs are similarly subject to resource limitations, such as the prevailing scarcity of medical laboratory professionals.

During the first stages of the COVID-19 and mpox epidemics, there was a notable rise in testing turnaround times when labs relied on a limited number of national laboratories. The extended duration required to get findings has a detrimental effect on the quality of patient treatment. Patients residing in rural regions would have a more significant impact as a consequence of logistical difficulties and delays in transporting samples to reference labs (18, 20).

Another potential issue that might have a detrimental effect on health equality is the potential decrease in the value offering of regional or local laboratory testing due to the ongoing provision of LDTs at local hospitals, particularly prominent academic medical institutions that may function as a multi-hospital healthcare system. The FDA's anticipation that hospital administrations would shoulder the substantial financial and personnel responsibilities necessary to adhere to the FDA's plan should be balanced with the actual circumstances. Hospitals are selling their clinical laboratories to national standard laboratory networks due to financial difficulties caused by decreased reimbursement and other obstacles. However, this has had a negative influence on the standard of medical treatment (18, 21). If implemented, the regulation has the potential to expedite the process of consolidating and acquiring local labs by national, corporate laboratories. In our perspective, the cessation of LDTs may expedite the loss of regional and local testing, so exacerbating

the issue of limited availability of testing and consequently diminishing health equality.

Furthermore, there has been a notable rise in the occurrence of new infectious illnesses and their corresponding epidemics in the last several decades. The occurrence of these outbreaks is characterized by their unpredictability, with a significant number of them taking place in local or regional areas. It is important to note that these outbreaks may not initially or ever escalate to the extent of a public health emergency, such as the emergence of multidrug-resistant organisms, Candida auris, quickly proliferating Mycobacterium, dengue, and arboviral encephalitides. The suggested regulation imposes limitations on our capacity to promptly conceive and execute LDTs aimed at tackling locally developing infectious illnesses of significant clinical importance, hence disproportionately affecting historically marginalized regions.

The Pew Foundation forecasts that around 12,000 medical laboratories conduct LDTs due to insufficient infrastructure, including FDA and laboratory facilities (22). The exact number of LDTs conducted per laboratory and the total number of tests is uncertain. However, it is safe to estimate that there are more than 100,000 LDTs that could be affected by the proposed regulation. Despite the suggested staggered strategy for submission and assessment, it is estimated that the annual submission volume would amount to several thousand LDTs. From our observations throughout the COVID-19 EUA reporting procedure, it is evident that the FDA presently lacks the necessary capacity and infrastructure to handle a large volume of applications. User fees, as explained below, will not address all of these issues. The suggested third-party review mechanism must possess a high level of resilience in order to accommodate the large volume of initial submissions. The failure to promptly evaluate submissions will result in a significant delay in obtaining necessary tests for patient treatment. The possibility of a substantial increase in applications may inadvertently result in a protracted evaluation procedure for commercial diagnosis vendors.

The hospital labs are deficient in the essential infrastructure required to facilitate the FDA submission procedure, including financial and personnel resources. The proposed regulation entails billions of US dollars in expenditures, with only a portion of these expenses being

covered by user fees. Diagnostic labs are now facing financial difficulties, mostly attributed to the implementation of the Protecting Accessibility to Medicare Acts (PAMA) in 2014. This legislation resulted in a significant reduction of compensation for routine laboratory tests, with a reduction of up to 59% (23). Laboratories are experiencing greater strain to maintain their existing workloads as a result of significant personnel deficiencies that have been further intensified in the aftermath of the COVID-19 pandemic (24). The average staff vacancy rate was 8.5%, with some places seeing as high as 25%. Rural regions were especially affected by this issue (25). It is anticipated that these issues will increase due to the retirement of an aging workforce and the diminishing number of medical laboratory technicians in the pipeline (24). The logistics, processes, and nomenclature related to FDA approval/clearance of LDTs are unknown to most medical and public health labs. Institutions aiming to get FDA approval or certification for their LDTs will need supplementary personnel with specialized knowledge in regulatory matters. Laboratories will be compelled to cease testing if they lack the necessary resources and regulatory proficiency to make an FDA application for an LDT under the IVD pathway. Consequently, either all testing will be submitted to a standard laboratory that has the necessary capabilities to submit their test, or the diagnostic gap will be widened.

The assertion made by the FDA about the hospital administration's capacity to provide the requisite resources for adherence to the proposed rule is erroneous. Hospital administrations that are cautious about taking risks would be reluctant to provide the necessary resources to manage the ambiguities of the evolving regulatory environment, particularly if mistakes might lead to FDA inspection or penalties. Reference labs may determine that they cannot endorse the submission of low-volume, esoteric tests due to the requirements connected with LDT submission. This situation will result in a nationwide emergency in the field of infectious illness diagnosis.

In order to boost Congressional funding and guarantee the FDA's ability to reach device approval objectives, user charges are collected from corporations for medical devices controlled by the FDA through the Medical Device Amendments of 1976. The Medicinal Device User Fee Acts (MDUFA) was first enacted in 2002 and undergoes periodic reauthorization spanning five years, during which corporations

engage in rate renegotiations. The proposed regulation by the FDA suggests that user fees would be imposed on LDTs, and the enforcement of this rule aligns with the subsequent renewal of the MDUFA. The FDA has proposed the potential application of the small company exemption within the program to not-for-profit labs, with the aim of reducing or eliminating costs. However, we express significant apprehensions about the development and execution of a user-fee system for LDTs. Clinical microbiology and health care labs now function inside healthcare institutions with limited financial resources and do not prioritize profit generation. The inclusion of educational, autonomous, and hospital-based labs inside the same business classification as commercial enterprises, despite the existence of a small company exemption, might be seen as unfair. The imposition of these costs will serve as a further incentive for labs to stop the development of infectious disease-specific test LDTs.

The distinction among CMS/CLIA and FDA testing verification standards has been established by the FDA. While the FDA mandates clinical validity, it is not expressly mandated as an aspect of test verification by CMS/CLIA. Clinical labs often depend on published research that demonstrates clinical validity for several LDTs. Although this assertion may not have proven true a decade ago, there exists a substantial body of published material that substantiates the clinical validity of the majority of LDTs now used in the field of infectious disease diagnostics. The independent establishment of clinical viability for a novel LDT via a clinical trial exceeds the capabilities of medical and public health labs. In the context of non-marketed LDTs used at a single institution, it is essential for the FDA to establish explicit guidelines pertaining to the acquisition of clinical validity evidence.

The new proposed regulation removes a risk-based method, unlike the 2014 FDA advice and the suggested VALID legislation. The classification of de novo LDTs remains unclear, despite the existing risk-based class I, II, and III scheme. From our perspective, the medical device classification system is not suitable for infectious disease laboratory diagnostic tests (LDTs). In contrast to cancer and pharmacogenomic testing, the majority of infectious disease tests exhibit a low level of risk, especially when conducted in labs that possess substantial expertise in using LDTs and the corresponding quality systems. This claim is based on the observation that in the diagnosis of infectious illnesses, it is often not possible to rely on a singular

test that provides a conclusive diagnosis and guides a patient's course of treatment. Multiple screening methods are often requested for infectious disorders, including society, antigen or nucleic acid identification, as well as serology.

The use of each test outcome, whether it be IVD or LDT, is then integrated within the framework of other outcomes, in conjunction with the patient's medical history, risk variables, and exposures. Subsequently, the physician utilizes all the laboratory and clinical information available in the field of medicine to make a diagnosis and provide treatment to the patient, if necessary. Diagnostic tests for infectious diseases, such as LDTs, are only one instrument that need interpretation within the clinical framework.

According to the Organization of Public Health Laboratories, a surveillance clinical laboratory is defined as a laboratory that have the capability to analyze or refer samples that have the potential to include microbial pathogens. Sentinel labs serves as the initial point for interacting with a disease of public health significance, such as possible biothreat substances and pathogens with increasing antimicrobial resistance (AMR), when there is no complete public health network in place. The worldwide increase in vaccine-preventable illnesses may be attributed to a combination of reasons, such as vaccine refusals and disruptions in immunization regimens caused by the COVID-19 pandemic.

Furthermore, the phenomenon of climate change is facilitating the dissemination of illnesses beyond their conventional geographical boundaries. For the identification of acute illness caused by new and re-emerging pathogens including mumps, measles, and tickborne illnesses, there is currently a lack of FDA-approved or certified tests. Furthermore, the CDC's Antimicrobial Resistance Risks assessment (26) reveals that there is a lack of FDA-approved or certified AST technologies or boundaries for several infections that are of concern. AMR is a quickly evolving worldwide menace. The inability to identify emergent antimicrobial resistance (AMR) and provide antimicrobial susceptibility testing (AST) outcomes for novel antimicrobials not only hinders our capacity to identify and track AMR, but also obstructs our ability to promote antimicrobial management, perhaps contributing to the further advancement of AMR.

Another contemporary example pertains to multidrug-resistant Candida auris, a pathogen that is spread inside hospital environments and has the potential to induce severe invasive infections. The CDC highly advises against the application of PCR for prevention purposes. However, at present, there are no PCR-based assays that have been authorized or certified by the FDA for the identification of C. Auris and laboratories are compelled to depend on LDTs (27). Labs that exhibit reluctance or incapacity to traverse the FDA LDT procedure will forfeit their capacity to promptly detect M. The impact of TB originating from positive cultures on our capacity to control the transmission of this illness, both inside and outside healthcare facilities, remains uncertain.

The FDA's plan severely dissuades laboratories from creating LDTs for diseases that are of significant public health concern. The proficiency necessary for the development of LDTs played a crucial role in our reaction to the COVID-19 epidemic. During a period when public healthcare and national laboratory centers were inundated with testing requests and patients experienced significant delays in getting test results, clinical laboratories were able to use their expertise in LDTs to promptly provide patients with life-saving outcomes (20).

The FDA understands that there is a possibility that some labs may choose to abandon the market or cease supplying certain IVDs in order to avoid the expenses associated with adhering to FDA regulations (28). This would result in a dual impact, encompassing both the probable depletion of now used LDTs for identifying public health significance and the enduring erosion of LDT development proficiency in monitoring medical and public health labs. The new regulatory structure will result in the loss of the same knowledge that was beneficial to the country during the COVID-19 epidemic. The ultimate consequence will be the deterioration of the public health infrastructure over time, which will undermine our capacity to effectively address not just future pandemics but also the resurgence of ancient infections amidst vaccine skepticism and global warming.

Medical and public health labs devote significant effort and money towards maintaining the elevated standards of laboratory diagnostic tests (LDTs). As previously stated, this entails adhering to current CLIA regulations, conducting frequent competence assessments, and ensuring both internal and external supervision by suitably qualified board-certified

personnel. It is essential that any additional regulatory obligations are designed to enhance and complement existing systems, while ensuring that they do not jeopardize a vital element of healthcare inside the nation. Given the potential for significant adverse effects of the proposed regulation on the medical and health care laboratory environment, it is imperative to adopt a more rational and evidence-based methodology.

One may argue that some companies have exploited loopholes in the existing regulatory procedure for LDTs, but these instances do not accurately represent the broader clinical and public health laboratory environment. Considering the FDA's acknowledgment that its new approach may lead to decreased availability of timely testing for patients, it is necessary to establish an effort to gather the necessary data for developing a regulatory system that satisfies patients' requirements while really enhancing the quality of treatment. One potential first measure may be mandating the registration of all Laboratories Diagnostic Tests (LDTs) used in the provision of patient care. The registration process may include details on the overall approach, target organism(s), kinds of specimens, and test quantities, among other specified factors. Furthermore, laboratories should establish a system for documenting significant adverse occurrences as outlined by the FDA (29). In the pursuit of comprehensive data collection, it is essential to ensure that labs are not unduly burdened by the procedure. The data gathered has the potential to inform the formulation of a more suitable regulatory framework for LDTs.

5. Conclusion

The FDA's proposed regulation explicitly states its primary objective of promoting innovation and enhancing fairness and availability of testing, all while protecting the welfare of patients. Additionally, clinical and public health labs share these objectives. Implementing a regulatory framework that was largely designed for diagnostic producers with substantial financial and logistical capabilities seems to be an improbable approach to accomplish this objective. We advocate for a regulatory framework that guarantees the safety and efficacy of the most high-risk tests, while also allowing for adaptability that is in line with the practicalities of infectious disease testing. This approach will effectively benefit patients and

minimize any negative impact on the labs that perform these tests.

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