December 4, 2023

Robert M. Califf, MD
Administrator
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: “Medical Devices; Laboratory Developed Tests”

Dear Administrator Robert M. Califf, MD:

On behalf of the American Society for Clinical Pathology (ASCP), I am writing to provide our formal comments on the U.S. Food and Drug Administration’s (FDA) Notice of Proposed Rulemaking (NPRM) on “Medical Devices; Laboratory Developed Tests (LDTs).” ASCP represents more than 100,000 board certified pathologists, other physicians, and laboratory science professionals that lead the nation’s efforts to diagnose and screen for diseases, such as diabetes; breast, lung, and prostate cancer; COVID and more. ASCP is the world’s largest organization representing pathology and laboratory medicine.

While we commend the FDA for its commitment to quality patient health and welfare by attempting to ensure that LDTs provide accurate and reliable results, ASCP opposes the concepts outlined in the proposed rule. ASCP agrees that all laboratory tests, including LDTs, should provide accurate and reliable results. As a patient-centric organization, ASCP believes the FDA proposal could limit access to safe and essential testing services for patients, particularly pediatric and cancer patients and patients with rare diseases.

While the overwhelming majority of LDTs have a solid track record of advancing patient care safely and effectively, we are aware that some LDTs have suffered from performance issues or may be marketed inappropriately. Thus, while we agree that certain enhancements to LDT oversight could help abate concerns of poorly performing LDTs being used to inform patient care, we do not agree that this requires the extraordinary level of regulatory oversight proposed by the Agency. This rule will create significant regulatory challenges that most labs will be unable to accommodate and will undermine access to the testing patients need for optimum diagnosis and treatment. Moreover, quality patient care dictates that laboratories should be encouraged, not discouraged, to develop innovative test services like LDTs.

The following is a section overview of this letter:

- LDTs Fill the Void
- FDA’s Proposed Framework
- The Clinical Laboratory Improvement Amendments of 1988
LDTs Fill the Void

LDTs play a vital role in healthcare, as they are essential to the diagnosis and treatment of numerous diseases and conditions. Medical laboratories develop LDTs for a variety of reasons, such as meeting an urgent patient need, identifying an emerging infectious disease, and often because no suitable FDA-approved test is available.

LDTs frequently represent the first high-quality and effective diagnostics available for infectious diseases (and public health emergencies like COVID-19). Certain cancers (including pediatric cancers), like leukemia and lymphoma, may not be diagnosable with commercial, FDA-approved tests. Monitoring of drug levels with narrow therapeutic ranges (to ensure effectiveness and prevent toxicity) in some patients with organ transplants or receiving certain antibiotics would be difficult or impossible in real time without LDTs. When timely diagnosis and treatment is essential, laboratories often rely on LDTs when no FDA-approved alternatives exist. Therefore, ASCP believes the proposed rule, if implemented as written, would significantly disrupt the delivery of safe and essential testing services.

LDTs also include commercial tests that have been “modified” and validated per CLIA standards to ensure similar performance. These tests are modified for various reasons, including that the laboratory identified methods to improve the test, the test needed to be customized to the needs of the patient (a form of “personalized medicine”), the test needed to be performed on specimen types other than those originally approved by the FDA, and/or the requisite testing supplies are not available. Under its proposal, even the most basic test modifications could require premarket clearance and would put treatment decisions and patient care at risk by creating market consolidation and increasing the expense to laboratories. The proposed regulations could also affect initiatives involving personalized medicine such as pediatric oncology or other testing customized to specific patient populations.

FDA Proposed Framework

Under the proposed rule, the FDA would expand its regulations to make explicit that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act (FD&C Act) including when the manufacturer of the IVD is a laboratory. In conjunction with this
change, the FDA proposes to implement regulatory oversight over LDTs so that IVDs “manufactured” by a laboratory would generally fall under the same enforcement approach as other IVDs, except where meeting certain requirements under CLIA may be leveraged.

The FDA is proposing to phase in implementation of its rule in five stages over four years, after which IVDs offered as LDTs generally would be expected to meet applicable requirements. While the FDA states that it will not be adopting a risk-tiering approach, the preamble of the rule does rely on this terminology for purposes of explaining the phase-out of the Agency’s general enforcement discretion approach. There is no definition of these terms, however. Considering how the FDA uses these terms, it suggests the Agency equates low risk tests with Class I, medium risk tests with Class II, and high risk with Class III. This suggests that most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval.

The Clinical Laboratory Improvement Amendments of 1988
The debate about the FDA’s oversight of LDTs often seems to center on whether these tests are subject to federal oversight. Unfortunately, the media and others have on occasion inaccurately suggested that LDTs are not subject to federal oversight (See Opinion: Lab-developed tests are integral to patient care, Washington Post, October 22, 2023). In fact, LDTs are very closely regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988 and have been for decades. CLIA outlines “federal standards for all U.S. facilities or sites that test human specimens for health assessment or to diagnose, prevent, or treat disease (CDC)."

To ensure test quality, CLIA requires LDTs to undergo analytic validation (the process of determining whether a test can accurately and reliably identify a particular analyte). It also requires laboratories to follow specific, extensive, and detailed quality control and quality assurance procedures to monitor the accuracy and precision of a test during the pre-analytic, analytic, and post-analytic phases of testing. We note that several CLIA-deemed accrediting agencies also require evidence of clinical validity (the process of determining whether a test can accurately identify a specific clinical condition) as part of their validation activities. Because this is not specifically reflected in the CLIA regulations, we believe it, as well as other enhancements, need to be included in CLIA’s regulations.

Moreover, under CLIA, laboratories must demonstrate expertise in each test they offer via mandatory programs of external proficiency testing, including comparisons with peer laboratories, and sanctions (up to and including “cease test” orders) for tests that do not meet statutory proficiency standards. If laboratories are not in compliance with CLIA’s standards, CMS and/or its deemed accrediting agencies are empowered to provide corrective remedies.

Extend the Comment Period
As the Agency is aware, ASCP is one of many organizations that sought, and was denied, additional time to comment on this rule (See ASCP request, attached). These requests reflected the concern expressed by stakeholders within the pathology and laboratory community that
the original 60-day comment period was insufficient to provide appropriate comments on a rule of this scope and complexity. Sufficient time is needed for laboratories to assess the impact of FDA oversight to the development and ancillary staff and services associated with their LDTs. Given the four-year phase-out period the FDA is proposing, we maintain that quality patient care would be well-served by providing stakeholders with an additional 60 days to better understand the existing medical device regulations, analyze their implications for patients served by LDTs, and provide constructive comments.

This rule, if implemented, would arguably have a bigger impact on laboratory testing in the United States than any other federal regulatory initiative since the implementation of the CLIA (1988) regulations. The potential for unintended consequences is enormous; the FDA’s oversight of these tests should not be rushed. We note that on several recent occasions, the FDA has extended comment periods after stakeholder requests, here, here, here, and here.

Indeed, on this point the medical community is united, as the American Medical Association’s House of Delegates recently unanimously approved a resolution authored by ASCP calling on the FDA to extend the comment period by an additional 60 days (see attached). After hearing supportive testimony on the resolution from several groups, the House of Medicine agreed:

“given the breadth and complexity of regulations around laboratory developed tests... under the current deadline, those who would likely be directly affected by the proposed rule may not have the ability to fully assess and communicate the impact it would have on their practice and patients. Your Reference Committee agrees that while the FDA has already indicated that they do not intend to extend the comment period beyond the original deadline, it is appropriate for our AMA to advocate for the rulemaking process to follow previous precedents and allow for all those who wish to comment to be heard.”

During discussions with clinical colleagues, our members learned many were not even aware of the rule’s existence, much less its potential impact on their patients. Therefore, it is critical that more time is given to include clinical colleagues in the discussion who will be impacted by this rule (e.g., oncology, pediatrics, etc.) to prepare for implications to their practice.

Given the scope and impact that this rule will have on laboratory testing, we reiterate our request that FDA extend the comment period an additional 60 days to allow sufficient time to review and comment on the Agency’s proposal.

FDA’s Proposed Rule Cites Weak Evidence to Justify LDT NPRM
In a section titled Current Information Raises Serious Questions about Whether Patients Can Rely on IVDs Offered as LDTs, the FDA outlines its “evidence” justifying its proposed regulatory oversight of LDTs. It cites several studies and articles raising concerns about LDTs performance issues. Unfortunately, the FDA’s data gathering appears to consist almost entirely of anecdotal reports, without systematic or scientific analysis of the problem.
For example, the very first document the FDA cites is a 2015 report titled The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies (subsequently debunked in a report by the Association for Molecular Pathology\textsuperscript{1}). A common theme of the FDA’s report is the use by LDT developers of study populations that do not accurately reflect the prevalence of rare diseases in the population to derive test performance characteristics, thus underestimating false positive rates and overestimating positive predictive value (PPV) of a given test.

Interestingly, the FDA’s own standards for clearance or approval are often subject to the same type of bias. There are many FDA-approved or FDA-cleared assays that were validated clinically by sample sets that were not representative of true prevalence of the diseases for which they are testing, and therefore may overestimate an FDA-cleared test’s predictive value in day-to-day use. At the extreme, there are currently FDA-cleared tests for detection of acute infection with infectious agents no longer endemic in the US, for which the positive predictive value is close to zero. In other words, low predictive value is a known challenge in the detection of rare diseases by any laboratory test (FDA-cleared or not). Citing these limitations in performance only for LDTs is misleading.

In addition, the FDA outlines in this section several complaints about LDTs. Once again, these cases are anecdotal, lacking in systematic or scientific analysis of the problem. These complaints—mostly from patients—do not provide the level of detail necessary to determine if they are valid criticisms of the performance of the laboratory test to which they are addressed. Moreover, the FDA should have provided data comparing the performance and problems of LDTs with those of FDA-approved tests. But such information is completely absent from the NPRM.

Medical laboratories perform about 12 billion laboratory tests annually, and if only one percent are LDTs, then that equates to 120 million tests a year. If there was truly a problem with LDT’s, then the FDA should be able to provide far more robust data about LDT performance problems and adverse impacts on patients—especially given that LDTs have been in use since before the FDA gained authority over medical devices in 1976. In our opinion, the FDA has not provided the level and type of evidence necessary to justify a regulatory initiative of such massive proportions.

\textsuperscript{1} Association for Molecular Pathology, December 13, 2015, Facts FDA Ignored: An analysis of the FDA report, “The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies”
The Scope of the LDT Market and FDA’s Capacity to Review

One of our concerns with the proposed rule is whether the Agency has the capacity to review/approve the myriad of LDTs it plans to regulate. The FDA estimates there are 40,000 to 160,000 LDTs in existence and that 50 percent would require premarket approval.

Over the last few years, the FDA has approved fewer than 100 medical devices per year on average. Even if the Agency leveraged the New York State Department of Health Clinical Laboratory Evaluation Program (NYSDOH CLEP), the Veterans Health Administration (VHA), and certain third-party reviewers, it is hard to imagine how the Agency could meet its obligations to timely process all applications it receives, even though it is requiring user fees from clinical laboratories and IVD manufacturers at the time of submission. Moreover, requiring so many new tests to seek FDA approval in such a short timespan would also undermine the Agency’s ability to review traditional IVDs and other medical devices.

The resulting bottlenecks in securing test clearance and approval would have serious repercussions for patient care. And in cases where there are no FDA-approved alternatives, the repercussions would be particularly troubling. For example, patients with acute leukemia are faced with a medical emergency requiring prompt diagnosis and treatment, which are dependent upon testing currently available only as LDTs. As these individuals typically present at a late stage of disease, waiting for necessary tests to be performed by a reference laboratory could result in death. As support for our concern that referring testing to another laboratory for analysis will delay test results and patient care, we recommend the Rogers et al. article, *The Impact of Disruption of the Care Delivery System by Commercial Laboratory Testing in a Children's Health Care System*. If the Agency intends to move forward with this regulatory scheme, it must provide assurances that it can process and complete all applications within one year.

Grandfathering

In the proposed rule, the Agency states that it “expects that some stakeholders will suggest that FDA continue to maintain the current general enforcement discretion approach with respect to premarket review and some or all QS requirements for currently marketed LDTs or a subset of currently marketed LDTs (i.e., what some previously referred to as “grandfathering”).” The FDA’s language here suggests that the Agency is only interested in considering “grandfathering” for those tests it classifies as either Class I or II devices. Presumably, the FDA believes that Class III, and some class II, devices in use prior to the proposed rule must undergo premarket approval.

ASCP supports grandfathering of all LDTs in use prior to the release of the proposed rule — including those approved by the NYSDOH CLEP or the VHA. In addition, ASCP believes that the Agency should allow modifications of “grandfathered” tests without the need for a new PMA/PMN submission. If properly validated, this would promote quality patient care by incentivizing laboratories to make performance improvements, when appropriate, in any LDTs they currently offer.
ASCP supports enhanced visibility of LDTs clinically offered in the US, such as through a registry, as well as when adverse events occur with those tests. If the FDA receives data indicating that the performance of a particular LDT may pose immediate patient harm, the Agency should take enforcement action to protect patient health.

**Leveraging External Partnerships**

The FDA states it is “interested in and seeks comment on leveraging programs such as the [NYSDOH CLEP] or those within the [VHA].” ASCP would strongly support reliance on these external partners for any LDT oversight scheme. We request clarification whether the FDA would extend assays approved from those program(s) for use throughout the US, or whether such approval would be limited to the geographic or administrative boundaries for which those program(s) are currently limited (e.g., patients within the state of New York). We note that NYSDOH CLEP requires that laboratories licensed to perform testing for state residents provide evidence of analytic and clinical validity for each registered LDT. ASCP strongly supports the NYSDOH CLEP’s allowance that evidence of clinical validity can take a variety of forms, including published studies in the peer-reviewed literature, the use of clinical guidelines, etc. If the FDA finalizes this rule, we urge the Agency to provide similar flexibility with regard to how laboratories can provide evidence of clinical validity.

The FDA’s rule also raises the prospect of relying on third party reviewers for the review of 510(k) submissions. Provided the FDA’s approach for approving third-party agencies are governed by strict conflict of interest requirements, we do not object to this proposal. Given the size of the LDT market and the number of LDTs the FDA estimates would have to undergo the PMA process, we believe that reliance on additional partners is essential to reduce the significant regulatory challenges we anticipate will undermine patient access to testing.

**Methodology Specific Maintenance of Enforcement Discretion**

In its proposed rule, the FDA has proposed and/or sought input on maintaining or extending enforcement discretion for certain LDTs, such as “1976-type LDTs,” human leukocyte antigen (HLA) tests, immunohistochemistry, and tests used solely for forensic (law enforcement) purposes or public health surveillance.

**1976-type LDTs:** The FDA proposes to maintain enforcement discretion for “1976-type LDTs,” which the Agency defines as tests that use manual techniques (without automation) performed by laboratory personnel with specialized expertise; use components legally marketed for clinical use; and are designed, manufactured, and are used within a single CLIA-certified laboratory meeting the requirements under CLIA for high complexity testing. ASCP supports maintaining enforcement discretion for these types of tests.

Under its proposal, the FDA suggests that immunohistochemistry (IHC) tests that “involve no automated preparation or interpretation” could continue to benefit from its general
enforcement discretion approach. IHC tests represent one of the largest methodological classes of LDTs and are absolutely critical to patient care. It is imperative to quality patient care that IHC be covered by the FDA’s general enforcement discretion approach. Moreover, while the FDA’s proposal of enforcement discretion for IHC tests is greatly appreciated, the vast majority of pathology laboratories providing these essential patient services do not use manual staining and, therefore, their LDTs would not be covered under the FDA’s general enforcement discretion approach. If the FDA finalizes this proposed rule, it is imperative that all IHC testing, regardless of how specimens are stained, are covered under the Agency’s general enforcement discretion approach.

**Human Leukocyte Antigen Typing:** The FDA proposes to maintain enforcement discretion for these tests (except for blood transfusions), provided they are "designed, manufactured, and used in a single laboratory certified under CLIA that meets the requirements to perform high-complexity histocompatibility testing when used in connection with organ, stem cell, and tissue transplantation to perform HLA allele typing, for HLA antibody screening and monitoring, or for conducting real and 'virtual' HLA crossmatch tests." ASCP appreciates the FDA proposing to provide enforcement discretion for HLA testing. These tests are critical to patient care, particularly for patients being cared for in an acute care facility. As these tests often need to be “customized” to the needs of the patient, requiring premarket approval, or even notification, could prevent patient testing.

ASCP has no objection to the FDA’s proposal to extend enforcement discretion to LDTs used solely for forensic (law enforcement) purposes or for public health surveillance,

**Other Test Methodologies:**
ASCP notes that there are other types of laboratory tests that the FDA is not proposing to cover under its general enforcement discretion approach that we believe the Agency should also cover under this approach.

One example that was brought to our attention by our colleagues at the International Clinical Cytometry Society is flow cytometry, which should be included for the same reasons that support retaining enforcement discretion for HLA testing. Flow cytometry is complex testing. It needs to be done locally because patients need timely access to this testing for urgent life-saving situations. Prompt medical care decisions are made based on this testing methodology, so rapid turnaround time (within hours of a patient presenting) is imperative. We believe that Rogers et al. explains the delays that would occur if testing had to be referred to another laboratory for analysis. We note that the vast majority of these tests are LDTs, with many used for Leukemia and Lymphoma, including for pediatric patients, so again, the need for enforcement discretion for these tests is significant.

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2 The FDA does not propose to extend enforcement discretion to lateral flow tests, as “they do not generally rely on laboratory personnel expertise.”
Another class of tests we believe would require continued enforcement discretion is therapeutic drug monitoring. These tests are only available as LDTs for certain medications. Under the FDA’s proposal, transplant patients could have to wait days to establish therapeutic drug monitoring levels. Such a delay could allow rejection of a transplanted organ that would have been avoided with rapid testing.

We anticipate that other types of tests will need to be covered by the FDA’s general enforcement discretion approach. To ensure patient access to critical testing, the FDA should not finalize this rule without a process in place to rapidly extend enforcement discretion to other kinds of LDTs.

Hospitals and Academic Medical Center LDTs
ASCP believes that LDTs developed by hospital and academic medical center (AMC) laboratories are fundamentally different from those of other LDTs. Traditionally, hospital and AMC laboratories developed LDTs in response to physician requests for assistance with caring and treatment for their patients, and we recognize that LDTs developed in these laboratories are not the driving concern for the FDA’s oversight. Due in large part to the costs and burdens associated with the FDA’s medical device approval system, some companies opted to develop a laboratory and provide testing services rather than seek FDA approval to sell their devices. It is our understanding that it is this segment of the LDT market that has prompted most of the FDA’s concern.

Without some sort of regulatory flexibility or exemption for AMCs and hospital laboratories, it is unclear how laboratories at these sites will be able to continue to provide these services to their patients. These laboratories lack the financial resources and personnel necessary to successfully navigate the FDA’s medical device regulations. We anticipate the prospect of requiring these sites to undergo the PMA/PMN process is sufficient to cause many of them to discontinue developing and utilizing these testing services. As commercial device manufacturers cannot possibly meet all patient testing needs, the loss of hospital and AMC LDT development and utilization will surely undermine patient access to testing and quality care.

An unintended consequence of the FDA’s proposal would be to eliminate or significantly delay the ability of AMCs to adequately train pathology residents. A key component of pathology residency education is understanding how laboratory tests are developed and validated. Understanding high-complexity testing requires knowledge of testing technical performance, limitations, and relevance to clinical care through statistical analysis and determination of reference ranges. LDTs at residency training centers are a critical pathway for producing competent pathologists who can interpret laboratory data, and this is recognized by the Accreditation Council for Graduate Medical Education (ACGME) via official core competencies from their ACGME Program Requirements for Graduate Medical Education in Anatomic Pathology and Clinical Pathology [3 examples follow]:
- Educational Program/ACGME Competencies/Patient Care/Anatomic and Clinical Pathology/Appropriate and Effective Consultation Program Requirement: IV.B.1.b).(1).(a).(iv) Residents must demonstrate competence in providing appropriate and effective pathology services consultation.

- Educational Program/ACGME Competencies/Patient Care/Anatomic and Clinical Pathology/Interpreting Laboratory Data Program Requirement IV.B.1.b).(1).(a).(ii) Residents must demonstrate competence in interpreting laboratory data as part of patient-care decision-making.

- Educational Program/Curriculum Organization/Anatomic and Clinical Pathology/Test Method Validation and Verification Program Requirement IV.C.10.a).(12) Resident experiences must include education in testing method validation and verification.

In its proposal, the FDA asks whether there should be a different policy for AMC laboratories. Because of the limitations on hospital and AMC laboratories, these entities would need less resource intensive requirements than the FDA’s current medical device requirements. ASCP believes that the FDA should maintain enforcement discretion for 510(k) premarket notifications/premarket approvals, quality systems regulation, and labeling requirements in AMC settings, while CMS compiles information on the use of LDTs currently in use in clinical laboratory settings. This could provide the HHS with performance metrics that the Agency could use, on a case-by-case basis, to investigate those LDTs warranting closer examination. Moreover, the FDA may wish to condition any regulatory flexibility it provides here to those entities offering LDTs prior to the release of the proposed rule.

Enhancements of CLIA are also needed, such as requiring laboratories to document clinical validity of their LDTs. This, we believe, would be complementary to the FDA’s oversight of LDTs.

Clinical Validity
One of the issues related to providing additional oversight of LDTs concerns their analytical and clinical validity. Analytical validation is the process of determining whether a test can accurately and reliably identify a particular analyte, while clinical validation is the process of determining whether the test can accurately identify a specific clinical condition in a given patient.

The FDA’s 2014 draft framework for LDT oversight included a section entitled “Evaluation of Clinical Validity of LDTs” in which the Agency asserted that it “…expects that for many LDTs, clinical validity has already been established in literature.”

Moreover, the text states that “FDA emphasizes that it is the Agency’s practice to leverage such information from the literature in lieu of requiring additional studies to demonstrate clinical validity. In these cases, the FDA may

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3 Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)
Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories
still require studies demonstrating device performance (e.g., analytical evaluations) but generally intends to rely on the scientific literature to support clinical validity if appropriate.” The ability to rely on scientific literature to document clinical validity is a matter of critical importance to the laboratory community, but no such statement or assurance is included in the current proposed rule.

Given that many LDTs currently offered or in development may not have a legally marketed device upon which to base a determination of substantial equivalence, the absence of the 2014 assurance raises concerns that the FDA may now plan to require full premarket review for such LDTs. We find this very concerning. The clinical trials infrastructure and financial resources required to undertake such studies simply do not exist within hospital, AMC, and smaller regional laboratories. As a practical matter, not allowing laboratories to utilize scientific literature to document clinical validity would lead to an acute shortage of needed testing for patients.

In the proposed rule, the FDA raises the prospect of leveraging the New York State Department of Health Clinical Laboratory Evaluation Program (NYSDOH CLEP), the Veterans Health Administration (VHA), and certain third-party reviewers, all (or most) of which already require documentation of clinical validity. It is our understanding that NYSDOH CLEP allows evidence of clinical validity to take a variety of forms, such as using published studies in the peer-reviewed literature, the use of clinical guidelines, etc. If the FDA finalizes this rule, we urge it to provide similar flexibility to allow these laboratories to meet patient needs.

LDTs, the Practice of Medicine, and the LDT NPRM’s Impact on Workforce
ASCP is concerned that the language in the proposed rule could interfere with the practice of medicine, as developing new and improved testing services is central to the practice of pathology, laboratory medicine, and pathology residency programs. ACGME standards state in its definition of the pathology specialty that pathologists “…develop new testing methods using patient tissues, blood, cells, and body fluid specimens.”

This is further reflected in pathology residency program literature. For example, residency program literature from the Department of Pathology, Molecular and Cell-Based Medicine at the Icahn School of Medicine at Mount Sinai notes this about its residency program:

“Our clinical laboratories are state-of-the-art, emphasizing new test development to improve the care of patients in our hospitals and clinics. Our laboratory medicine team was on the front line when COVID hit New York, quickly developing and implementing new tests for COVID-19 detection and a quantitative COVID-19 antibody test...Whether by using data generated in the clinical laboratories to develop better testing or treatment algorithms, developing new mass spec-based diagnostic tests, or developing new AI-enabled tools to improve diagnostic accuracy, we provide the opportunity to use your skills to make the world a better place, one patient at a time.”
If the FDA adopts a final rule that undermines the ability of pathologists and other laboratory medicine professionals to practice medicine or of medical schools and residency programs to train pathologists, other physicians, and non-physician laboratory medicine professionals, it could hamstring the development of competent pathologists for the future and damage patient access to quality patient care throughout the United States.

Unintended Consequences
ASCP is concerned that the FDA does not appreciate the scale of the regulatory burden that the proposed rule would impose on the pathology and laboratory medicine community. In consulting ASCP’s membership about the likely impact of this rule, we have repeatedly heard concerns that few hospital, AMC, or local/regional medical laboratories have the financial resources or personnel to handle the regulatory burden proposed by the FDA. These laboratories will cease to provide LDTs or will drastically reduce their LDT offerings, which will, in turn, greatly restrict patient access to treatment and care.

This impact will not be uniform: rural and underserved communities will be hit hardest. Patients served by smaller laboratories, including those doing larger volumes of LDT testing, may cease operating, and there is no guarantee that national reference labs will fill the void. To a certain degree, these impacts may be disease- or condition dependent. For conditions like acute leukemias and aggressive B-cell lymphoma, such as Burkitt lymphoma, patients can currently get same-day diagnostic confirmation and an immediate start to therapy by being served locally. For these and other urgent diagnoses, some patients cannot afford to wait to begin treatment because their test results have been delayed due to being sent to a large reference laboratory.

We expect that this rule will also exacerbate personnel shortages within the pathology and laboratory medicine workforce, as the need within medical laboratories for individuals with these skills will diminish. To continue working on test development, these professionals may have to leave the laboratory sector. Moreover, as test development is central to the practice of pathology and laboratory medicine, we are also concerned that this proposal could impact the quality of the practice of pathology and laboratory medicine. Further, as LDT development is central to how residency programs provide training on disease diagnosis, the loss of these tools could diminish the quality of the resident training experience and/or reduce the attractiveness of the pathology profession. This would exacerbate pathologist shortages. As healthcare personnel tend to seek employment in urban areas, these personnel issues are most likely to be felt in rural and underserved areas.

Moreover, the loss of these skills within pathology and laboratory medicine could also adversely affect medical research. Pathologists and laboratory professionals with expertise in test development are often called upon to develop new tests to identify previously undiagnosed diseases or assess the impact of potential therapies. Diminishing their test development skill set will diminish research, and it will slow the pace of medical discovery.
will also reduce the number of individuals qualified to evaluate tests in the way that the FDA plans to evaluate tests.

**ASCP Recommendations**

While we recognize that certain types of LDTs could benefit from additional regulatory oversight, we believe this proposed rule will adversely impact the overall quality of patient care and drastically undermine diagnostic innovation in the United States. The FDA lacks the capacity to quickly and efficiently conduct the number of PMA reviews it is proposing. While the FDA generally reviews fewer than 100 diagnostic devices per year, it is proposing to require PMA submissions for approximately 50 percent of a market the Agency estimates at 40,000 to 100,000 LDTs—beginning just 3½ years after adoption of a final rule—and without grandfathering of existing tests. Even at the low end of the FDA’s estimate on the number of LDTs in use, it is hard to fathom that this proposal will not cause massive disruptions for patient access to testing. The loss of access to testing will lead to missed/delayed diagnoses, inadequate treatments, and poorer patient outcomes.

It is highly speculative whether the FDA’s estimates on the scope of the LDT market are accurate. CMS does not currently curate a public database of LDTs in current use, so the overall numbers of LDTs, their uses, their performance characteristics, etc., is unknown to the broader public. This “unknown” presents a substantial risk to patient access to testing and quality care should the Agency move forward with this rule. Consequently, we believe that the FDA should NOT finalize this rule but that the U.S. Department of Health and Human Services should develop an LDT database to begin the process of evaluating the LDT market for any future regulatory initiatives.

This registry should be fully accessible to the public, so that physicians and researchers may be able to better understand the LDT market and how these diagnostics perform relative to other IVDs.

In addition, ASCP believes that the Agency should not require minor modifications of FDA-approved tests (e.g., use serum instead of plasma, allow for dilutions, etc.) to undergo any sort of Agency required filings or review. Given the need for expediency of testing for certain patients, this will cause unnecessary delays in diagnosing and treating patients. We believe that modifications would be better handled under the CLIA framework. We further recommend that the Agency specifically exclude modifications of FDA-approved tests from its definition of an LDT.

Finally, ASCP is providing an addendum (see attached) comprised of several documents we have developed over the years outlining our views on LDTs. We believe this illustrates our commitment and dedication to working toward a solution that is focused on improving the quality of patient care and the diagnostics used to improve optimum patient outcomes.
ASCP appreciates the opportunity to provide comments on this important issue. If the Society can be of assistance, please do not hesitate to contact me at President@ascp.org or Matthew Schulze, Senior Director of the ASCP Center for Public Policy, at Matthew.Schulze@ascp.org.

Sincerely,

Robert A. Goulart, MD, MASCP
President, ASCP

Attachments
Robert M. Califf, MD  
Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002  

RE: Request for Extension of 60-Day Comment Period for CMS Proposed Rulemaking Medical Devices; Laboratory Developed Tests  

Dear Commissioner Califf:  

On behalf of the American Society for Clinical Pathology (ASCP), I write to respectfully request that the U.S. Food and Drug Administration (FDA) extend the comment period for the recently proposed rulemaking on Laboratory Developed Tests (LDTs) and to hold a public meeting explaining the specific requirements with which medical laboratories will have to comply to secure FDA approval of their LDTs. The 60-day comment period specified in the proposed rule is insufficient to provide medical laboratories with a meaningful opportunity to comment.  

The proposed rule would transfer oversight of LDTs from the Centers for Medicare & Medicaid Services (CMS) to the FDA. The rule would impose a massively complex, new oversight paradigm to the development and use of LDTs by medical laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Given almost 50-years of general enforcement discretion by the FDA, during which the Agency rarely exercised oversight over LDTs, few laboratories have experience with or understanding of the intricacies of FDA’s vastly different oversight scheme for approving medical devices. With FDA estimating that 50 percent of LDTs would require premarket approval under its proposed oversight approach, the proposed rule will massively disrupt medical laboratory operations in U.S. hospital and academic medical center laboratories.  

To add to the confusion for stakeholders, the proposed rule does not outline in detail the specifics of all the FDA regulatory requirements to which CLIA-certified high complexity medical laboratories would be held. Nor does it explain how medical laboratories will be expected to navigate the duplicative and potentially conflicting FDA and CMS (CLIA) requirements. The result is that the medical laboratory community does not fully understand how this proposal will impact their operations nor how they will be able to provide appropriate comments on it.  

We note FDA has not held any public meetings on LDT oversight in nearly a decade. Given the lack of clarity on the specifics of how FDA would provide oversight, minimize duplicative regulatory burdens, and/or resolve regulatory conflicts between FDA and CMS, a public
meeting is imperative to enable the medical laboratory community to respond with appropriate and well-reasoned comments.

The Office of the Federal Register’s A Guide to Federal Rulemaking notes that “For complex rulemakings, agencies may provide longer time periods such as 180 days or more.” FDA’s proposal is clearly complex rulemaking. On several recent occasions, FDA has provided a 120-day comment period, such as for its June 28, 2022, proposed rule “Nonprescription Drug Product with an Additional Condition for Nonprescription Use.” Accordingly, ASCP urges FDA to extend the comment period to 120 days and to host a public meeting (not less than 60 days before the comment deadline) to educate laboratories on the specifics of the regulatory requirements FDA plans to impose.

We recognize and appreciate the goal of prompt rulemaking. However, the proposed rule creates significant potential for unintended consequences, which could adversely impact patient access to testing and cause irreparable harm to laboratory operations throughout the United States. Given that FDA’s proposal is intended to "help assure that patients are receiving accurate and reliable diagnostic test results," this warrants a thoughtful, careful approach to imposing an entirely new regulatory framework on this critical industry.

ASCP appreciates the opportunity to provide comments on this important issue. If the Society can be of assistance, please do not hesitate to contact me or Matthew Schulze, Senior Director of the ASCP Center for Public Policy, at Matthew.Schulze@ascp.org.

Sincerely,

Marsha C. Kinney, MD, MASCP
President, ASCP

cc: Xavier Becerra, JD, Secretary, U.S. Department of Health and Human Services
Richard L. Revesz, JD, MS, Administrator, Office of Information and Regulatory Affairs, Office of Management and Budget
Whereas, the federal Food and Drug Administration (FDA) mission includes the responsibility for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and

Whereas, the FDA has previously communicated that it believes that the FDA has the authority to regulate laboratory developed tests (LDTs) as medical devices (in vitro diagnostic products – IVDs) under the Medical Device Amendments of 1976; and

Whereas, since 1976 FDA has chosen to practice enforcement discretion, not requiring premarket approval or clearance for clinical laboratories to design and perform LDTs within the regulations set forth in the Clinical Laboratory Improvement Amendments of 1988 (CLIA); and

Whereas, on October 3, 2023, FDA published to the Federal Register a proposed rule that would end this enforcement discretion and would require all LDTs to be approved or cleared as manufactured medical devices, effective at the time of finalization of the rule based on a four-year, five-step phase in period; and

Whereas, previous proposed rules by FDA, and drafts of proposed legislation, have provided for more reasonable measures to assure appropriate clinical validation of LDTs under FDA oversight; and

Whereas, LDTs play a crucial role in day-to-day medical care, including (but not limited to) the establishment of immunophenotypes for appropriate classification and treatment of leukemia and lymphoma, determining genetic and genomic status for purposes of determining appropriate treatment and appropriate screening per current standards of care, advanced chemical analysis methods for rapidly changing toxicology and therapeutic drug monitoring needs, tissue typing for transplant, and others; and

Whereas, many clinical laboratories currently offering LDTs lack the infrastructure to meet the compliance standards suggested in the proposed rule, and enforcement of the rule would therefore risk loss of access to clinically necessary laboratory testing; and

Whereas, LDTs have historically played a significant role in the development of new tests and diagnostic tools, implementations of the proposed regulations could impede the ability of laboratories to adapt quickly to emerging health threats and hinder the ability to conduct diagnostic advancements; and

Whereas, specific areas within laboratory medicine, including histocompatibility (HLA) and forensic testing, have been granted exemptions under new federal regulations, acknowledging
the anticipated challenges to ongoing patient care in transplantation and law enforcement, it is therefore reasonable to consider that similar adjustments or leniencies in the proposed regulations could prove beneficial in other medical fields; and

Whereas, current federal law (CLIA) already requires all laboratory tests (including LDTs) to meet very stringent and specific criteria for analytical validation of test performance characteristics prior to offering these tests to patients; therefore be it

RESOLVED, that our American Medical Association submit a comment to the FDA proposed rule entitled “Medical Devices; Laboratory Developed Tests” (Published October 3, 2023) requesting a 60-day extension period to the current comment period.

Fiscal Note: (Assigned by HOD)

Received:
REFERENCES

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RELEVANT AMA POLICY

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February 2, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) Draft Guidance, Document No. 1739

FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs) Draft Guidance No. 1738

Dear Sir or Madam:

The American Society for Clinical Pathology (ASCP) is pleased to submit the following comments regarding the draft guidance documents from the U.S. Food and Drug Administration (FDA) entitled Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs), Draft Guidance No. 1739, and FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs), Draft Guidance No. 1738, issued October 3, 2014. These documents describe the FDA's risk-based framework for addressing the regulatory oversight of a subset of in vitro diagnostic devices (IVDs) referred to as laboratory developed tests (LDTs). ASCP is a professional medical society that provides excellence in education, certification, and advocacy on behalf of patients, pathologists, and laboratory professionals. ASCP's over 100,000 members include pathologists and laboratory professionals, many of whom develop and perform LDTs.

Clinical laboratory testing is an essential component of medical practice and patient care. Laboratory developed tests (LDTs), diagnostic tests that are developed, validated, and used for in-house pathology and diagnostic purposes, are already substantially integrated into standard practice for diagnosing and managing disease, and informing decisions about lifestyle and behavior. These tests enable improved prevention, diagnosis, treatment and disease management and prevention for an array of common chronic conditions such as cancer, heart disease, and diabetes, as well as rare genetic disorders and infectious diseases. They have become indispensable tools in the practice of medicine.

ASCP firmly believes that LDTs, as with all laboratory tests, should be of the highest quality and provide valid and useful information for clinical decision-making. ASCP applauds the FDA’s concern for patient health and welfare by trying to ensure that LDTs provide accurate and reliable results. Like the FDA, ASCP considers verification of both analytical and clinical validity for all IVDs, including LDTs, to be fundamental to quality patient care. While supportive of the FDA's specific attention to “high risk” testing as a focal point, ASCP believes that the Clinical Laboratory Improvement Amendments of 1988 (CLIA) provides the best starting point for regulating these tests. However, in the absence of oversight by CMS, ASCP could support a limited role for FDA in the oversight of LDTs, provided the framework coordinates seamlessly with current CLIA requirements.
and is not overly burdensome for laboratories. By limited role, ASCP means that FDA should limit its oversight of LDTs to only those tests that may be characterized as “high-risk.”

While it is a fact that there are many more LDTs in use today than when Congress enacted the Medical Device Amendments (MDA) in 1976, these assays, with rare exception continue to have a solid record of advancing patient care safely and effectively. In light of this, ASCP feels that the Agency has not provided sufficient evidence to justify the extensive regulatory effort outlined in these guidance documents. We note that Executive Order 12866 states that “Federal agencies should promulgate only such regulations as are... made necessary by compelling public need... (emphasis added)” Many of our members have expressed concern that increased and duplicative oversight could result in the unintended consequence of disrupting critical patient testing needs, and dramatically hinder the development of new diagnostics. ASCP feels that the proposed framework is vague and overly burdensome for laboratories and appreciates this opportunity to identify some areas of concern. ASCP strongly urges the FDA to exercise prudence with regards to the scope and enforcement of these guidance documents to ensure that the nation’s patient testing needs are not in any way disrupted.

Specific Issues of Concern in the Guidance

LDT Definition and Scope of Guidance

The draft guidance documents define the term laboratory developed test (LDT) as “an IVD that is intended for clinical use and designed, manufactured, and used within a single laboratory.” ASCP considers the terminology used in this definition to be both problematic and incorrect for the vast majority of tests targeted for this proposed framework. LDTs are tests, not “devices”, and they are performed, not “manufactured,” through a set of prescribed procedures. For a more accurate definition of LDTs, ASCP urges FDA to consider the definition for LDTs found in the Modernizing Laboratory Test Standards for Patients Act of 2011 (H.R. 3207), which defines LDTs as “tests developed and performed by a clinical laboratory solely to furnish clinical laboratory testing services for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of human beings...” This definition further distinguishes LDTs developed and performed by laboratories from IVD manufacturers by specifying that they are not otherwise introduced into interstate commerce.

ASCP is also concerned about the Agency’s intent to classify FDA-approved or -cleared tests that have been modified as new LDTs, thus requiring resubmission. The universe of such tests is significant and ASCP believes the FDA lacks the resources to process and approve these tests in a timely manner. If FDA is intent on regulating modified FDA-approved or -cleared devices, ASCP urges the Agency to adopt the definition for “modification” used by the New York State Department of Health, Wadsworth Center, Comprehensive Test Approval Policy and Submission Guidelines. Using their definition, a modification or change from intended use would include a change in (1)...

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1 The term “regulation” used in this Executive Order (EO) is defined as “an agency statement of general applicability and future effect, which the agency intends to have the force and effect of law, that is designed to implement, interpret, or prescribe law or policy or to describe the procedure or practice requirements of an agency. It does not, however, include: Regulations or rules issued in accordance with the formal rulemaking provisions of 5 U.S.C. 556, 557. Therefore, we believe the E.O. is applicable to the Agency’s proposed guidance documents.
specimen type; (2) the type of analysis (e.g., qualitative versus quantitative); (3) the purpose of the
 assay (e.g., screening, diagnosis, prognosis, monitoring and/or confirmation); or (4) the target
 population(s). It would not include minor adjustments in test procedures such as extending sample
 stability criteria, changing quality control materials, or using a new instrument model. Mandatory
 resubmission for modifications that are appropriately regulated and validated under CLIA would
 only serve to cripple the laboratory industry as well as the FDA and would simply not result in
 higher quality care for patients.

Furthermore, situations in which an LDT is performed at different laboratories under the same
 ownership using a common Standard Operating Procedure should necessitate only one submission,
 and not a separate submission for each site. Moreover, multiple laboratories under common
 ownership should not result in a LDT being erroneously classified as an “IVD” (rather than LDT),
 subject to the regular pre-approval process.

ASCP is further concerned that the FDA may be significantly underestimating the numbers of
 laboratories and tests that would be subject to this framework and questions the workflow
 capacity of the Agency to adhere to the proposed timeline in the guidance given their broad
 definition of an LDT. Lengthy approval procedures could have a devastating impact on patient care
 by delaying the implementation of new tests, hindering innovation, increasing development and
 compliance costs, and thus limiting patient access to potentially beneficial assays. Bear in mind
 these workflow issues will delay non-LDT IVD approvals as well. For these reasons, ASCP believes
 that LDT’s that have already been approved or cleared by the New York State Department of Health
 Wadsworth Center be grandfathered, including FDA-approved tests for which the intended use has
 been modified that are deemed to be high-risk.

Characterization of Clinical Laboratories as “Manufacturers”

The 1976 Medical Device Amendments to the Federal Food, Drug and Cosmetic Act (FD&CA)
 granted the FDA authority to regulate medical devices, including IVDs. IVDs are defined as reagents,
 instruments, and systems intended for use in diagnosing disease or other disease conditions, as
 well as health status.2 IVDs are packaged products developed, marketed, and sold by medical device
 manufacturers involving interstate commerce. The Agency’s regulation of IVD focuses on the
 manufacturer’s claims regarding the device’s clinical “intended use,” efficacy and safety.

Clinical laboratories perform laboratory tests, the results of which may become an integral part of
 many medical decisions, providing clinicians with often pivotal information necessary for the
 prevention, diagnosis, treatment, and management of disease. The draft guidance uses the following
 example to describe the process by which a “typical” LDT is developed and ultimately performed on
 patients.

“A laboratory uses peer reviewed articles to guide development of a new diagnostic
device. The laboratory uses general purpose reagents and analyte specific reagents
combined with general laboratory instruments and develops a testing protocol, that
together constitute a test system which is then verified and validated within the

2 Code of Federal Regulations, Title 21, Volume 8 [21 CFR 809.3]
laboratory. Once validated this device is used by the laboratory to provide clinical diagnostic results."

While this description accurately characterizes the process by which the development of these tests occurs, this process does not result in the manufacture of a “device” or a “physical product.” Therefore, many of the requirements in the proposed framework and the core of FDA expertise do not readily transfer to the processes used in the development and performance of an LDT by credentialed pathologists and laboratory professionals in a CLIA-certified laboratory.

The development and performance of an LDT by a clinical laboratory for a patient is a medical service. If that test is not performed properly using established quality practice standards or an erroneous result is obtained and used to inform patient care, the laboratory becomes subject to medical malpractice claims rather than strict product liability lawsuits. CLIA’s mandate to monitor quality and the standards of testing processes (analytic validity through accuracy and reliability) as well as the laboratory professionals that perform LDTs offers more appropriate framework, which ASCP believes could enhanced to better ensure that patients receive quality services.

Laboratories simply do not meet the definition of a manufacturer when they develop and perform LDTs. They are not “manufacturing” devices intended for commercial distribution through interstate commerce, and therefore should not be subject to manufacturing practice standards or to the product liability claims that may be alleged based on the FDA definition of an LDT. Just as clinical labs are not the same as device manufacturers, medical devices are not exact proxies for LDTs. To recognize these distinctions, the requirements must be right sized in the context of the differences between devices and LDTs, and laboratories vs. manufacturing plants. The differences are significant, and these requirements dramatically alter the regulatory landscape for the laboratory industry. Therefore, requirements should be a flexible, interactive, and transparent process for the Agency and the industry to maximize patient safety.

Perceived Gaps in Regulatory Oversight of LDTs

ASCP firmly believes that the best interests of patients are served by evidence-based laboratory medicine and that all laboratory tests should be clinically and analytically valid, performed by properly certified/accredited laboratories and competent laboratory professionals, and the results interpreted by properly trained clinicians. Under CLIA, laboratory directors and technical supervisors are responsible for ensuring that test methods are both appropriate for the intended clinical application and provide quality results. Laboratories are inspected, certified, and accredited under CLIA by CMS or independent accrediting bodies. CLIA oversight focuses on accuracy and reliability of the testing process, with specific requirements for analytic quality control, proficiency testing, qualifications of laboratory testing personnel, requirements for reporting results, and appropriate documentation of standard operating procedures. All laboratory tests are classified according to their level of complexity (waived, moderate, and high), on which CLIA bases specific regulatory requirements for laboratories performing tests in those categories. These tests are performed in laboratories under the direction of highly trained and competent laboratory professionals, including pathologists and laboratory scientists.

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CLIA’s regulatory oversight system enables clinical laboratories to modify FDA-approved tests and develop their own tests (LDTs) provided they validate the performance characteristics of these tests. To ensure that laboratories adhere to these requirements, these data are reviewed through routine inspections performed under the auspices of CLIA. This framework has allowed timely and appropriate introduction of innovative testing into practice and has been instrumental in providing quality patient care when an FDA-approved test is not available.

Furthermore, it is important to note that clinical laboratories are also currently subject to various state regulatory requirements. ASCP urges FDA to be mindful that the requirements of this proposed framework must be harmonized with both the federal CLIA regulating agencies and state requirements, thus alleviating the possibility of laboratories being subject to confusing, duplicative, and perhaps conflicting requirements. The need for harmonization is reinforced by several executive orders, including Executive Order 12866, which mandates that, “Each agency shall avoid regulations that are inconsistent, incompatible, or duplicative with its other regulations or those of other Federal agencies.”

ASCP is also concerned that the draft guidance documents fail to specify how the FDA intends to ensure laboratory compliance with FDA quality system regulations (QSRs), since LDT laboratories are not actually manufacturers. How will FDA integrate these systems intended for a manufacturing facility into a clinical laboratory? How will the FDA differentiate among the various steps that are present in performing a lab test such as the acquisition of a patient specimen from a third party, specimen transportation and storage, technical aspects of preparing a specimen for analysis, medical interpretation of the result(s) and specific communication between the lab and ordering physician, including reflex testing. It is unclear who will do the inspections. Will FDA utilize personnel trained to inspect “manufacturers” or will personnel knowledgeable with clinical laboratories and their operations be used? It is also unclear how FDA inspector training be provided and funded.

What sanctions does the Agency plan to use (e.g., Form 483 citations, warning letters, suspension of their CLIA certificate, fines etc.) for laboratories that are found to be in violation of these policies? ASCP recommends that if the FDA should begin enforcing these regulations, a review by the Government Accountability Office be conducted within a year. The purpose of this review should be to evaluate what, if any, impact these new policies have on patient access to new technologies and the ability or willingness of laboratories to develop new testing methodologies.

**CLIA Modernization:**
As is outlined in these comments, ASCP has serious concerns about a number of elements of the Agency’s proposed guidance, which in its current form is unsustainable for the clinical laboratory industry. Given the breadth and nature of the CLIA’s regulatory mandates, we believe that the CLIA framework offers a more logical model for providing federal regulatory oversight of LDTs, especially those that are moderate and low risk. Compared to the CLIA model, the FDA plan is highly duplicative, unnecessarily burdensome, and does not seamlessly mesh with the way clinical laboratories operate under CLIA. Moreover, we do not believe that from a public policy standpoint it is appropriate for two different agencies to oversee the same aspect of the same industry (the performance of clinical laboratory testing). Indeed, such jurisdictional overlaps should be minimized if not avoided altogether. We note Executive Order 13610 holds that “Each agency shall avoid regulations that are inconsistent, incompatible, or duplicative with its other regulations or those of other Federal agencies.” This is especially odd in light of the fact that both agencies operate under the U.S. Department of Health and Human Services.
That said, we do not believe that CLIA, and by extension CMS, currently provides sufficient oversight over LDTs to ensure patient safety. Consequently, ASCP calls on CMS to immediately finish the process initiated by FDA to enhance the regulatory oversight of LDTs by modernizing the CLIA regulations. ASCP believes this enhanced regulatory oversight requires additional CMS staff who would be tasked with monitoring and reviewing LDT performance data submitted through an LDT registry (See below).

**Risk-based Approach Toward Oversight of LDTs**

ASCP supports a risk-based regulatory scheme for LDTs as the most logical approach; however, there must be clearly established guidelines regarding how the FDA will classify which tests are subject to FDA oversight. The criteria established by FDA should ensure that there will be minimal confusion and appropriate classification of LDTs. While high-risk LDTs could fall under the purview of the FDA, ASCP believes that those tests not classified as high risk should continue to be regulated by CMS under an enhanced regulatory scheme.

Along these lines, ASCP supports that any LDT that has obtained approval or clearance from the State of New York Department of Health Wadsworth Center, be grandfathered under the FDA guidance document.

ASCP recommends that FDA issue guidance for the risk classification of LDTs that are subject to public comment and then duly published before the Premarket Review and other requirements, such as Quality Systems Regulation (QSR) requirements, are applied to clinical laboratories. It is essential that laboratories know which LDTs are considered by the FDA to be high-risk, before they are required to comply with Registration and Listing and other requirements, such as QSR and Adverse Event Reporting. Determining LDT risk classification prior to the submission of a PMA application, if necessary, will allow laboratories to adequately plan and prepare to minimize the likelihood that critical patient testing services will be interrupted. It will also substantially diminish the huge compliance costs that would be associated with securing FDA approval for those LDTs that need not seek FDA review. This will also minimize the potentially massive increase in administrative workload that the FDA would encounter as a result of potentially thousands of applications for approval.

ASCP recommends that the definition for modifications to FDA high-risk tests that may result in review be narrowly defined to be no more encompassing than the New York definition (see page 3 of this comment letter). Using any other definition of modification (e.g., extended sample stability, changes in control materials) that could result in a resubmission to the FDA would both cripple the industry as well as the FDA with significant risk to patient care. FDA should focus its limited resources on the highest risk tests, in particular, those tests that assist in selecting treatment for a serious or life-threatening disease or disorder and for which such information is the "sole determinant" for directing or changing clinical treatment and an incorrect result could have a significant adverse impact on patient outcome or public health. ASCP believes that other modifications are appropriately regulated and validated per CLIA.

ASCP applauds FDA's intent to use a public process for classifying and prioritizing existing LDTs. FDA has indicated they will use an advisory committee to recommend how LDTs should be classified with regard to risk. A broad representation of stakeholders on this committee will be
essential to ensure a logical approach that considers multiple perspectives. Among the stakeholders participating should be pathologists and laboratory scientists of various subspecialties (particularly molecular pathology) from a variety of settings (hospital laboratories, academic medical centers, small clinical laboratories, large national reference laboratories, sole-source proprietary laboratories); ordering clinicians, also from various subspecialties (oncology, infectious disease, etc.); representatives from the IVD manufacturing industry; representatives from FDA, CDC, CLIA, and accrediting bodies; and patients who have benefited from access to those LDTs.

**Enforcement Discretion for Unmet Needs, Rare and/or Infectious Diseases**

ASCP recommends the FDA continue to exercise enforcement discretion with respect to Premarket Review requirements for unmet medical needs until several commercial tests are available. Having only one option available may require laboratories to purchase expensive equipment for low volume testing, therefore discouraging the use of such tests. Continued enforcement discretion until multiple testing options are available will provide laboratories much needed flexibility to select tests that are appropriate for their operation and patient population.

The guidance states that FDA recognizes that some LDTs will meet the criteria for a Humanitarian Use Devices (HUD) thereby qualifying for the Humanitarian Device Exemption (HDE). An IVD may qualify for HUD designation when the number of persons who may be tested with the device is fewer than 4,000 per year. ASCP is concerned that a cut-off of 4,000 patients is too low for laboratories to maintain testing, and urges the FDA to instead, raise this number to appropriately accommodate incidence for rare diseases. This cut-off is of particular concern in the area of newborn screening. While conditions such as PKU have an incidence of one in 10,000 live births, under the proposed framework, PKU testing would fail to qualify for the HDE. All 50 states in the United States require newborn screening for PKU. ASCP urges FDA to adopt the FDA Center for Drug Evaluation and Research’s current definition of rare disease from the 1983 Orphan Drug Act as diseases that affect no more than 200,000 patients nationwide.

ASCP also recommends that FDA continue its policy of broad enforcement discretion for LDTs used to diagnose and monitor infectious diseases. There are numerous examples of infectious disease LDTs that preceded the availability of FDA-cleared or approved assays, often by many years, to benefit patients and protect public health. Overly burdensome regulatory requirements could present significant risks to public health by increasing the time needed for assay development during pandemics and other emerging infectious disease scenarios.

**Notification/Registration and Listing**

Under the draft guidance, notification for LDTs is required to begin 6 months after the issuance of the final guidance. However, the actual classification process for LDTs remains unclear, and it appears the requirement for notification occurs in advance of LDTs being classified. It is essential that the laboratory industry know which LDTs are considered by the FDA to be high-risk before they are required to comply with any Registration and Listing that may ensue after initial notification and other requirements (Adverse Event Reporting and QSR) in order to plan appropriately and avoid the disruption of testing services for patients. Applying these requirements before an LDT is risk classified we believe is unreasonable and overly burdensome for laboratories.
**Registry:**
In order for FDA and/or CMS to effectively provide oversight of LDTs and to focus this oversight on the highest risk LDTs, we believe that it is imperative to establish a LDT registry, which could be modeled on the NIH's Genetic Test Registry. Such a tool should be populated with each LDT's key performance metrics, such as analytical and clinical validity, to assess the test and determine its associated risk level. In an ideal world, the registry could also include data on clinical utility though we recognize that is outside of the boundaries of the FDA draft guidance plan. As outlined elsewhere in this letter, we believe that it is critical that each test's risk level be identified prior to any requirement to submit the test for approval to minimize the related administrative burdens and costs of compliance. To minimize the burden on clinical laboratories, the registry should also be structured to seamlessly integrate with each clinical laboratory's compliance requirements under CLIA. A registry could be very useful for patient care as it could provide clinicians with a query function to enable them to better identify those LDTs that would be most appropriate to their patients. A registry would also provide greater transparency with regard to the universe of LDTs and their applicable risk level.

Another benefit of the registry is that it could be used as a far less costly and burdensome alternative, both for the agency and for affected stakeholders (including IVD manufacturers), than the outright PMA approval scheme outlined by the Agency in its proposed guidance documents. Rather than moving forward with the proposed guidance, a registry could enable the agency to maintain enforcement discretion and target those high risk LDTs that pose the greatest potential for significant patient harm.

**Medical Device Reporting (MDR) Requirements**

ASCP recommends the FDA more clearly define what is subject to adverse event reporting beyond the current User Facility requirements. ASCP believes that the FDA's requirements for adverse event reporting should not delve into issues of medical practice, such as test interpretation, pathological analysis by physicians, use of laboratory generated data by physicians, technical preparation, and shipment and handling of specimens for laboratory analysis. These criteria must specify where the technical and medical components begin and end, situations covered by user facility reporting, and what specifically laboratories will be required to report to the FDA.

It is also important to note that adverse event reporting due to malfunction of FDA regulated products is already required under the User Facility reporting requirements. Therefore, there should not be an additional reporting requirement placed on laboratories where adverse event reporting is covered under the User Facility regulations.

**Premarket Review Requirements**

ASCP urges the FDA to proceed cautiously in determining the scope of assays affected by this framework and recommends that the Agency streamline the Premarket Approval (PMA) process to reduce processing times. In addition, ASCP recommends FDA thoroughly review the present premarket notification process, 510(k), as well as the PMA/de novo processes to determine if, in fact, they are truly appropriate for LDTs.
Again, under this framework, we strongly believe that the classification of LDTs into high and non-
high-risk categories must be completed before the PMA review and other requirements such as
QSR are applied. It is essential that the laboratory industry know which LDTs are considered by the
FDA to be high-risk before they are required to comply with Registration and Listing and other
requirements (Adverse Event Reporting and QSR) to plan appropriately and avoid the disruption of
testing services for patients. Applying these requirements before an LDT is risk classified we
believe is unreasonable and overly burdensome for laboratories.

ASCP is also concerned that mandating pre-market approval before deploying new LDTs could
undermine the ability of laboratories to develop innovative diagnostics. This is specifically a
concern for low-volume tests, such as those for rare disorders, which have historically been
developed at smaller laboratories and academic medical centers. Therefore, ASCP opposes any
policy change that would bar laboratories, in toto, from marketing LDTs during the approval phase,
unless FDA can determine during initial review that a particular LDT poses significant potential for
harm. ASCP also urges the Agency to allow clinical laboratories to perform modified FDA-approved
IVDs— provided they can document the analytical and clinical validity of their modifications—
without the requirement for premarket notification. The universe of such tests is significant, and
FDA lacks the resources necessary for timely approval, thereby potentially undermining the
incentive and ability to offer innovative, high-quality diagnostics, which could therefore be
detrimental to patient care.

**Quality Systems Regulation Requirements**

ASCP has several concerns regarding how the FDA intends to apply QSRs to LDTs, and specifically
how those requirements would coordinate with existing CLIA and state requirements. QSR more
aptly applies to true manufacturers to assure that products are safe and effective for use. Clinical
laboratories are not analogous to device manufacturers, just as the development of an LDT is not
analogous to the production of devices. ASCP strongly recommends the FDA must work closely
with the laboratory industry to determine how to implement QSR appropriately for clinical
laboratories. For example, there are many terms used in QSR that carry very different definitions in
a clinical laboratory environment (e.g., validation versus verification). ASCP urges the FDA to
crosswalk current CLIA requirements with regard to document control; records management;
materials management; training and competency; equipment calibration, quality and maintenance;
verification and validation; etc., to determine if they satisfy QSR. There are many aspects of quality
and control that CLIA and QSR share. ASCP urges the FDA to examine these commonalities carefully
and devise a framework that allows clinical laboratories to leverage their current CLIA-compliant
processes and procedures to meet FDA QSR requirements in the least burdensome manner.

**Summary**

The practice of pathology and laboratory medicine is currently in a tremendously dynamic phase,
particularly with regard to genomics. When discoveries at the research bench translate to the
clinical bench, patients benefit by receiving care that is personalized and selective. When this
occurs, our primary objective as health care providers is realized—to deliver the right treatment to
the right patient at the right time.
As our knowledge base in this area increases and feeds the development of important new diagnostics, the regulatory framework applied must take into account the impact it may have on this process. FDA oversight should not impinge on the practice of medicine. Laboratory medical directors and their professional staff are acting within their expertise as credentialed pathologists and laboratory scientists as they interact with ordering clinicians to develop and perform LDTs.

In summary, ASCP recommends the following with regard to the regulation of LDTs by the FDA:

1. Limit any FDA oversight of LDTs to high-risk LDTs only; defining such tests that assist in selecting treatment for a serious or life-threatening disease or disorder and for which such information is the “sole determinant” for directing or changing clinical treatment and a incorrect result is likely to have a significant adverse impact on patient outcome or public health; moderate and low risk LDTs should continue to be under the purview of CLIA.

2. Grandfather of any and all LDTs approved by the New York State Department of Health, Wadsworth Center, including FDA-approved tests for which the intended use has been modified that are deemed to be high-risk.

3. Determine risk categories for current LDTs with prior to Registration and Listing requirements or compliance with QSR.

4. Develop a registry to enable the risk categorization of an LDT to determine the need to submit a PMA.

5. Permit laboratories to continue performing LDTs during the approval phase, unless FDA can determine during initial review that a particular LDT poses significant potential for patient harm.

6. Harmonize FDA’s guidance with CLIA’s regulatory framework to avoid unnecessary duplication, particularly for inspections and quality systems design.

7. Perform a GAO review within a year of implementation to evaluate impact of new policies on patient access to new technologies and the ability or willingness of laboratories to develop new testing methodologies.

As a patient-centric organization, ASCP shares the FDA’s mission to protect patient safety. ASCP agrees that regulatory oversight is essential to ensure that all diagnostic tests offered to patients are of the highest quality, reliability, and safety, and that each test should provide valid and useful information for clinical decision-making. At this early stage of the genetic diagnostic era, it is vital that FDA strike the right balance in asserting their authority over the regulation of laboratory developed tests. The regulatory infrastructure adopted must be sufficiently meticulous to safeguard the public without being so burdensome that it impedes emerging technology.

ASCP appreciates the opportunity to present these comments. If we can be of further assistance, please feel free to contact me through Andrea Bennett, Director, ASCP Center for Public Policy at 202-347-4450.

Sincerely,

William G. Finn, MD, FASCP
President, ASCP
Regulation of Laboratory Developed Tests (LDTs)
(Policy Number 10-02)

Policy Statement

The American Society for Clinical Pathology (ASCP) believes that laboratory developed tests (LDTs), as with all diagnostic tests, should be of the highest quality, reliability, and safety, and that each test should provide valid and useful information for clinical decision-making.

Background and Rationale

For years, the diagnostics industry, clinical laboratories, researchers and patient groups have debated the appropriate regulatory scheme for LDTs. LDTs play a vital role in health care and their potential impact on patient care will increase dramatically in the coming years. There must be assurances that LDTs, particularly high-risk LDTs, provide clinically relevant information to physicians and patients. Yet LDTs present some unique regulatory questions. How do regulators establish fair, concrete, predictable regulatory requirements for LDTs that will protect the public’s health but not deter innovation or unduly hamper access to tests? ASCP believes that the regulatory oversight of LDTs should be under the purview of the appropriate federal agencies and an independent, neutral third party reviewer in a process unfettered by any conflicts of interest.

ASCP supports a clearly defined risk-based regulatory scheme that carries provisions that permit appropriate and timely responsiveness in a public health crisis.

I. Introduction

A. Definition and Use of Laboratory Developed Tests

Laboratory developed tests (LDTs) are in vitro diagnostic tests that are developed, validated and used for in-house pathology and diagnostic purposes. LDTs are intended for use only by the laboratory entity where they are developed, unlike the majority of commercially marketed laboratory tests which are manufactured by medical device companies and sold to laboratories, hospitals or physicians’ offices in interstate commerce, and must be cleared or approved by the Food and Drug Administration (FDA) through either the premarket notification or premarket approval (PMA) processes. Laboratories that develop these “in-house” diagnostic tests, either create the necessary reagents themselves or purchase reagents from outside vendors, and then develop their own proprietary test. These tests are never sold to other laboratories, hospitals or doctors, and therefore have not typically been subjected to FDA approval or clearance processes. FDA-approved commercially marketed tests that have been modified in any way by a laboratory are also considered to be LDTs and subject to the same regulations applied to all LDTs.

Because this very common definition for LDTs is also quite broad, it could potentially include a number of common diagnostic laboratory tests including microscopic examinations, microbiology culture and susceptibility tests, staining and examination of tissue sections, and blood cross-matching procedures. These tests are well established diagnostic laboratory tests with adequately demonstrated clinical validity and utility. Some of these tests may also be available as commercially marketed laboratory tests and therefore subject to the regulations governing that category. However, most LDTs are molecular genetic tests for which there is no commercial test available.

The Clinical Laboratory Improvement Advisory Committee (CLIAC) Genetic Testing Good Laboratory Practices Workgroup describes these LDTs as encompassing “a broad range of laboratory tests performed to analyze DNA, RNA, chromosomes, proteins, and certain metabolites using biochemical, cytogenetic or molecular methods or a
combination of these methods.” These LDTs are used to detect heritable or acquired disease-related genotypes, mutations, or phenotypes for clinical purposes.”

B. Current Oversight Authority

Oversight of laboratory tests in the U.S. is provided by a still-evolving system that currently includes government agencies, health care payers, professional associations, and other stakeholders. With the passage of the Federal Food, Drug, and Cosmetic Act (FDCA) and Clinical Laboratory Improvement Amendments (CLIA), the U.S. Congress established provisions for the oversight of various aspects of laboratory medicine. Passage of the Medical Devices Amendments Act in 1976 granted the FDA jurisdiction over commercially distributed test kits as in-vitro diagnostic devices. The FDA claims the statute also grants them jurisdiction over the regulation of LDTs. However, the agency issued a draft guidance in 2006 announcing that, with the exception of a small subset of LDTs deemed to be “in vitro diagnostic multivariate index assays” (IVDMIAs), the agency would exercise enforcement discretion, reasoning that most LDTs were simple, low risk diagnostic tools that were well-characterized. In addition, most LDTs were reliant upon various FDA-regulated individual components, either analyte specific reagents or general reagents, and the tests were performed in CLIA laboratories certified to conduct high complexity testing.

II. Justification for Enhanced Regulatory Oversight

LDTs, initially used to diagnose rare diseases and conditions, were intended to be used within a single institution by physicians and pathologists actively engaged in their patients’ care. In recent years, LDTs have become increasingly more complex, and their use has expanded to assess high-risk, but relatively common diseases and conditions. However, as LDTs have begun to assume a more pivotal role in medical decision-making, they are more frequently being performed in geographically distant commercial laboratories instead of within the patient’s health care setting under the supervision of a pathologist and treating clinician. In some instances, LDTs are being marketed directly to the patients. ASCP is concerned that due to the increased application of LDTs for genetic testing and personalized medicine, the use of LDTs outside of the physician-patient context, and the development of LDTs by larger corporations, that some LDTs may not have been properly validated for their intended use, putting patients at risk for missed diagnosis, wrong diagnosis, and inappropriate treatment.

For more than a decade, during a period of greatly accelerated advances in molecular pathology and increased growth of clinical applications of LDTs, various groups have examined the need for strengthening Federal oversight of genetic testing and testing laboratories. In 1997, the Task Force on Genetic Testing, convened jointly by the National Institutes of Health (NIH) and the U.S. Department of Energy (DOE), issued Promoting Safe and Effective Genetic Testing in the United States, which made several recommendations regarding the oversight of genetic tests and testing laboratories. In its review of current practices at the time, the Task Force concluded that, “sometimes, genetic tests are introduced before they have been demonstrated to be effective, and useful,” and “there is no assurance that every laboratory performing genetic tests for clinical purposes meets high standards.” The report also noted deficiencies in the informational materials available to help providers and patients interpret results. In this report, the Task Force recommended the development of a framework for ensuring that new tests meet criteria for safety and effectiveness before they are unconditionally released, thereby reducing the likelihood of premature clinical use.

Between 1998 and 2000, the Clinical Laboratory Improvement Advisory Committee (CLIAC) recommended the enhancement of regulations governing the quality of clinical laboratories generally and genetic testing laboratories specifically. In 2000, the Centers for Disease Control and Prevention considered adding a genetic testing specialty under regulations of the Clinical Laboratory Improvement Act Amendments of 1988 (CLIA). Later that same year, the Secretary’s Advisory Committee on Genetic Testing (SACGT) issued Enhancing the Oversight of Genetic Tests, which concluded that additional oversight of genetic tests was warranted and should be achieved through new multifaceted and innovative oversight mechanisms.
SACGT also agreed with CLIAC that a genetics specialty should be added to CLIA. In 2003, the CLIA regulations were amended in several general ways, but the Centers for Medicare & Medicaid Services (CMS) did not proceed with adding a genetics specialty.9

In 2008, Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS) published U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services, an extensive report about the oversight roles of Federal, State, and private sector entities concerning the analytical and clinical validity of genetic tests, private sector responsibilities for clinical laboratory accreditation, standard setting, and the development of clinical practice guidelines for genetic testing. The Committee identified gaps in oversight in a number of areas, including, (1) the regulations governing clinical laboratory quality; (2) the oversight of the clinical validity of genetic tests; (3) the transparency of genetic testing; (4) the level of current knowledge about the clinical usefulness of genetic tests; and (5) meeting the educational needs of health professionals, the public health community, patients, and consumers, along with providing tools to assist these groups with the interpretation and communication of genetic test results. To help close the gaps in oversight related to clinical validity, which would help assure the appropriate use of laboratory tests, the Committee recommended that “the FDA should address all laboratory tests, regardless of how they are produced (i.e., as a commercial test kit or laboratory-developed test), in a manner that takes advantage of its current experience.”10

While LDTs represent the leading edge of clinical testing being offered to patients today, and most have a solid record of advancing patient care safely and effectively, ASCP agrees that the time has come for the FDA to insert its regulatory authority over high risk LDTs. There must be assurances that these tests are clinically valid, performed correctly by competent laboratories, and the results communicated to patients by clinicians adequately trained to interpret them. ASCP supports strengthened oversight to ensure that LDTs remain one of the key tools clinicians can use to answer increasingly complex questions regarding patient care.

The FDA itself suggests that its policy of enforcement discretion may have disincentivized innovation by manufacturers who must seek FDA approval, yet it also acknowledges the dependence of innovation upon an appropriate oversight framework, particularly in areas such as genomics, genetic testing, and diagnostics for rare diseases, areas in which medicine is highly reliant upon LDTs. In the Agency’s states that, “In these and other categories, it is important that FDA provide a reasonable, predictable, and consistent regulatory policy for ensuring the safety and effectiveness of LDTs and provide sufficient time for implementation. Therefore, enhanced regulation should encourage innovation, improve patient outcomes, strengthen patient confidence in the reliability of these products, and help reduce health care costs.” 11

III. Other Regulatory Models

As federal agencies seek to develop a new regulatory paradigm for LDTs, it will be important to adopt a global perspective. With the formation of multinational companies and global markets for their products, innovation in genomics clearly transcends national boundaries. International research is being conducted by such groups as the Human Genome Organisation (HUGO) and the Human Proteome Organisation (HUPO), and there are transnational regulation and standard setting initiatives underway by other organizations such as the International Conference on Harmonization (ICH) and the International Organization for Standardization (ISO).12

While the United States is home to more consumer genetic diagnostic companies than any other country, regulatory oversight of LDTs, particularly those marketed directly to consumers, is also under close scrutiny abroad. In Australia, Canada, and across Europe, a number of governmental committees and task forces have reviewed the oversight of genetic testing in their respective countries, and issued reports with similar conclusions: genetic tests should not enter clinical practice without thorough independent evaluation.
Achieving this universal goal would require addressing a number of regulatory deficiencies. While all of these countries employ a regulatory scheme based on risk classification, there are significant differences in how risk is defined and degree to which the regulation has been enforced. While LDTs in both Canada and the United States have generally not been subject to pre-market review procedures required of commercially marketed laboratory tests, there is more widespread support in Europe and Australia for a more consistent approach in private laboratories. However, in Europe, genetic tests, like nearly all diagnostic tests, are classified as low-risk, and are therefore exempt from pre-market evaluation. Public sector laboratories in Europe are exempt from the European Union’s In Vitro Diagnostics Directive, although an alternative mechanism for ensuring the clinical quality of LDTs occurs through professionally driven quality assessment schemes.

IV. Important Considerations in the Establishment of a New Regulatory Scheme

As federal agencies determine how best to assert their regulatory authority over high complexity LDTs, ASCP believes the following to be important considerations.

A. Regulating Bodies and Conflicts of Interest
The process to review the validation standards of LDTs must be unbiased and impartial, regardless of their risk stratification. It is imperative that there be no conflicts of interest or potential business relationships that would drive decision-making. Accrediting bodies should monitor the performance and quality of LDTs, but that role should be post-clearance, to avoid any conflicts of interest. The establishment of an independent, third party reviewer to develop and verify quality and accuracy of claims prior to review by FDA and the federal CLIA-regulating agencies would enhance the transparency of the process. This entity would be not-for-profit, non-governmental, non-accrediting, non-industry, and entirely neutral. Both public health and patient safety would be best served by implementing a centralized third party review system rather than a peer review model. In addition, strengthening federal government oversight through the FDA and CLIA processes is essential. This will require additional resources (e.g. staff and expertise), for both FDA and CLIA.

B. Risk-Based Regulation Scheme
While a risk-based approach to regulation is most logical, there must be clearly established guidelines regarding how the FDA will define which tests are subject to regulation. The criteria established by FDA should ensure that there will be minimal confusion and appropriate classification of LDTs. While high risk LDTs should fall under the purview of the FDA, lower risk LDTs, those not deemed to be “in vitro diagnostic multivariate assays” should continue to be regulated by CLIA. The development of an enhanced regulatory process of oversight should involve a combination of governmental and non-governmental organizations. The CLIA regulatory process must ensure that data is collected that substantiates claims of clinical validity.

C. Applying New Scheme to Existing LDTs
There must be assurances that all LDTs are clinically valid. However, the FDA should establish a regulatory framework that phases-in the requirements on those LDTs currently in use. This is necessary to ensure continued patient access to advanced diagnostics. For those LDTs that can demonstrate a history of current use, FDA should provide laboratories a reasonable period to demonstrate the clinical validity while at the same time allowing them to continue providing the assay for clinical purposes. Moreover, FDA should maintain the authority to suspend use of the test for diagnostic purposes if the Agency has a reasonable concern that it provides insufficient clinical validity. LDTs that cannot demonstrate a history of current use should go through the regular approval process.

D. Phase-In Period for new LDTs
Specific requirements regarding premarket review and quality systems should be phased-in over time to help facilitate predictability and planning within the laboratory community and industry. Implementation in a step-wise fashion could first require compliance for high-risk tests, and later implement requirements for moderate and low-risk tests.
An algorithm to prioritize FDA’s processing of premarket approval applications should be developed. Among those factors that we suggest should be included in such an algorithm are test volumes, severity of the condition or disease being tested, and impact the test can have on the treatment of the patient.

E. Proficiency Testing
Proficiency testing (PT) should be required for all non-waived genetic laboratory tests for which PT products are available, and the ASCP recommends that the Department of Health and Human Services fund studies to evaluate alternative performance assessment methods, such as certification and test-based continuing education. A balanced approach will be essential to evaluate the reproducibility of these assays with a protocol that maintains the advantages of multi-site PT, but also addresses the risks of inter-laboratory variation.

F. Clinical Validity and Utility
Evaluation of LDTs, as with any other diagnostic laboratory test, should include the test’s analytic and clinical validity. Clinical utility, however, remains a subjective standard dependent on how clinicians utilize assay results in managing patient treatment, and not on an objective quality inherent in the test method. Requiring proof of clinical utility as a pre-requisite for marketing of these assays might impede or even prevent patient access to them. A lengthy approval process that requires evidence of clinical utility might hinder the development of these assays, thus preventing researchers from implementing translational findings into clinical practice.

G. Impact of Lengthy Regulatory Processes
ASCP cautions that lengthy approval procedures could delay implementation of new tests, stifle innovation, increase development costs, and thus limit patient access to potentially beneficial assays. Low volume LDTs, such as those for rare genetic tests, could experience difficulty attaining approval because of the small populations that would be available for clinical trial testing. Moreover, smaller laboratories, particularly laboratories at academic medical centers that have historically been major sites of innovation for LDTs, could be forced to abandon this area of testing, precluding patients from cutting-edge therapeutics.

H. Emergency Use Authorization (EUA) Provision
The establishment of an Emergency Use Authorization (EUA) provision within the regulatory framework is recommended for protection of the public health in emergencies. Overly burdensome regulatory requirements could present significant risks to public health by increasing the time needed for assay development during pandemics and other emerging infectious disease scenarios. The EUA provision should focus on expediting the approval process for state and federal public health laboratories in times of crisis.

Conclusion
Laboratory developed tests or LDTs are increasingly being integrated into standard practice for diagnosing and managing disease, predicting the risk of developing disease, and informing decisions about lifestyle and behavior. These tests are enabling improved prevention, treatment, and disease management for an array of common chronic conditions such as cancer, heart disease, and diabetes, as well as rare genetic disorders. They have become indispensable tools in the practice of medicine. However, ASCP strongly believes that only high quality, clinically and analytically valid diagnostic laboratory tests should be offered to patients. As a patient-centric organization, ASCP’s mission is to protect patient safety while promoting advances in medicine. At this early stage of the genetic diagnostic era, it is vital that federal agencies strike the right balance in asserting their authority over the regulation of laboratory developed tests. The regulatory infrastructure adopted must be sufficiently meticulous to safeguard the public without being so burdensome that it impedes the emerging technology.
References


