



**Summary of testimony of Dr. Donald Karcher, MD, FCAP**

**President, College of American Pathologists**

**Before the House Energy and Commerce Committee's**

**Subcommittee on Health Hearing:**

***"Evaluating Approaches to Diagnostic Test Regulation***

***and the Impact of FDA's Proposed Rule"***

**March 21, 2024**

Laboratory-developed tests (LDTs) are tests developed and used in a single clinical laboratory to meet a specific clinical need because there is no U.S. Food and Drug Administration (FDA)-approved or FDA-cleared test. LDTs are typically developed for patients with rare diseases or to meet specific clinical needs in the patient population being served by the laboratory.

The CAP believes a balanced, risk-based approach to the federal oversight of LDTs is needed to promote continued innovation, meet patient needs, and ensure that each test is valid, safe, and reliable.

The CAP has advocated for three main principles for LDT oversight:

- Protect patients,
- Ensure continued access to safe and innovative diagnostic tests, and
- Develop a framework that is the least burdensome for pathologists and their laboratories.

The CAP cannot support the FDA proposed rule, published on October 3, 2023, without significant changes. If significant changes to the rule are not made by the FDA, the CAP urges Congress to pass the Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2023, which includes several CAP priorities. The CAP opposes making changes through legislation to CLIA and instead recommends continuing changes through the regulatory process.



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**Room 2123 Rayburn House Office Building**

**March 21, 2024**

Chair Cathy McMorris Rodgers, Chair Brett Guthrie, Ranking Member Frank Pallone, and Ranking Member Anna Eshoo, the College of American Pathologists (CAP) thanks you and your Committee for your leadership in organizing this bipartisan hearing to prioritize and understand the oversight of laboratory-developed tests (LDTs). The CAP looks forward to serving as a resource to the Committee on this topic and being an active and productive participant in conversations to develop policy in this space.

My name is Dr. Donald Karcher. I am President of the CAP, and Professor and Immediate Past Chair of Pathology at George Washington University (GW). I have been a practicing pathologist for more than 40 years, including as an Army pathologist for 8 years, in private community hospital practice for 2 years, and as an academic pathologist for most of my career. I served as Chair of Pathology at GW for 20 years. I've also served as Chief of Hematopathology, Chief of Flow Cytometry, and Director of Laboratories at GW. I received my residency training in Anatomic and Clinical Pathology at the Brooke Army Medical Center in San Antonio, Texas, and I am Board-certified in Anatomic and Clinical Pathology and Hematopathology. Before joining the GW Pathology faculty, I served as Chief of Hematopathology at the Walter Reed Army Medical Center in Washington, DC and Chief of Hematopathology at the Louisiana State University Medical Center in New Orleans.



The CAP is the leading organization of board-certified pathologists, serving patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide. Our members practice clinical and/or anatomic pathology in community hospitals, independent laboratories, academic medical centers, and federal and state health facilities. Pathologists are at the forefront of utilizing and developing new test methods and molecular analysis. This includes using molecular and genomic tests to predict and diagnose disease and to guide specific patient treatment and developing and using LDTs to predict risk of disease, diagnose disease, guide therapy selection, and assess a patient's response to a specific treatment. Utilizing teams of practicing laboratory professionals as inspectors, the CAP accreditation program helps laboratories maintain consistently high levels of service throughout all levels of laboratory operations based on rigorous and continually updated standards and requirements.

### **Laboratory-Developed Tests (LDTs)**

LDTs are tests developed and used in a single clinical laboratory to meet a specific clinical need. All clinical laboratories in the U.S. are already regulated under the Clinical Laboratory Improvement Amendments (CLIA), overseen by the Centers for Medicare & Medicaid Services (CMS). LDTs are developed almost always because there is no FDA-approved or FDA-cleared test that meets the specific clinical need in question. LDTs are typically developed for patients with rare diseases or to meet specific clinical needs in the patient population being served by the laboratory. By current regulation, an LDT can only be performed by the laboratory that developed it. These tests cannot be marketed or sold to be performed in another laboratory. Most LDTs are developed and used for patients being cared for in the hospital or health care network where the laboratory is located, allowing the laboratory and pathologists to interact directly with the physicians caring for the patient. Although many LDTs represent innovations in patient care, most utilize well-established laboratory methods that most medium and large size clinical laboratories already have experience using. The technology and clinical validity of the



majority of LDTs are already well-documented in the medical literature before the test is developed. The components of many LDTs, such as so-called analyte-specific reagents, are already individually regulated by the US Food and Drug Administration (FDA). While the FDA has asserted authority to regulate LDTs, the agency has exercised enforcement discretion. LDTs are currently regulated through the laboratory accreditation process as required by CLIA.

### **CAP Priorities for Oversight of LDTs**

Historically, LDTs were created manually by laboratory personnel and used within a single laboratory. As such, they were viewed by the FDA as “lower risk” tests and therefore not regulated. As time went on, they became far more complex, relying on high-tech instrumentation to derive results. Congress has been working for over a decade to find a proper balance between oversight and overburden. To that end, CAP believes a balanced, risk-based approach to the federal oversight of LDTs is needed to promote continued innovation, meet patient needs, and ensure that each test is valid, safe, and reliable. Through the years, the CAP has advocated for three main principles for LDT oversight:

- Protect patients,
- Ensure continued access to safe and innovative diagnostic tests, and
- Develop a framework that is the least burdensome for pathologists and their laboratories.

The CAP believes that a legislative and regulatory framework for LDTs should include a role for CLIA and the FDA, according to a test's risk level to a patient. To avoid duplication in regulatory requirements, the CAP believes that oversight of LDTs must include a tiered risk-based structure that requires the FDA to oversee high-risk LDTs while leveraging current laboratory reporting requirements to ensure the ongoing quality of medium- and low-risk LDTs. The concern with high-risk LDTs is that there is no transparency in how the results are obtained, such as when proprietary test algorithms are used to produce results, and no way for external verification of the accuracy of the results to be done, such as what happens with proficiency testing. With a high-risk LDT, the chance of a misdiagnosis and



subsequent impact on the patient's health is unacceptably high. Additionally, all LDTs should be required to meet analytical and clinical validity standards. Tests deemed low or moderate risk could be validated by independent third-party accreditation organizations to prevent undue delays in test offerings.

## **FDA LDT Proposed Rulemaking**

### **Background**

On June 14, 2023, the FDA filed a notice of proposed rulemaking for the oversight of LDTs with the White House Office of Management and Budget (OMB). The notice of proposed rulemaking filing was prompted after legislation concerning the oversight of LDTs had been thoroughly debated in 2022 but did not gain enough support to pass Congress. As a result, officials at the FDA said the agency would move forward with the formal regulatory process in the absence of congressional action. The proposed regulation was published in the Federal Register on October 3, 2023, and received 6,707 comments from interested stakeholders, including the CAP. The CAP's comments can be found here <https://www.regulations.gov/comment/FDA-2023-N-2177-6372>. As of this writing, the final LDT oversight rule is currently under review at OMB with an anticipated release date of next month.

### **CAP Position on the FDA's LDT Proposed Rule**

Because LDTs have been and continue to be critical for the advancement of medicine, **the CAP cannot support the current FDA proposal without significant changes. The current proposal will reduce the number of highly accurate LDTs available to patients and further delay timely patient care.**

Therefore, the CAP recommends that the proposed rule be modified as follows:

#### ***1. Enforcement Discretion***

Ending enforcement discretion for all LDTs and using the existing FDA framework for the regulation of LDTs, as written, will severely stifle medical innovation, increase regulatory burden on clinical laboratories, introduce unsustainable costs as part of the development of LDTs by clinical laboratories,



and hinder the delivery of potentially life-saving test results to patients. Therefore, the CAP recommends that the proposed rule be modified to continue FDA enforcement discretion of:

- Exempt tests offered prior to the rule's enactment,
- Forensic, Human Leukocyte Antigen (HLA), and Manual tests,
- LDTs Developed and Offered Locally by a Clinical Laboratory,
- Adverse Events Reporting,
- Quality Systems (QS),
- Corrective Action and Removal,
- Labeling

## ***2. Leveraging Existing Structures***

The proposed rule creates redundancies and overburdensome requirements because it fails to utilize existing laboratory reporting structures. As a result, laboratories will experience increased reporting and workforce costs, happening at a time when clinical labs are experiencing declining reimbursement and significant staffing shortages. To mitigate the cost and regulatory burden of compliance, the proposed rule should be amended to include:

- Public hearings to determine test risk classification and solicit input on test classifications as an ongoing process to advise the FDA on these classifications.
- Implementation delays in stages four and five until completion of a comprehensive educational campaign on the test risk classification requirements.
- General controls when LDTs are offered by special request to a laboratory from its local physician community and meet the following criteria:
  - Offering LDTs in small volumes;
  - Serving their local communities and actively involved in patient care;
  - Using well-characterized standard tests; and
  - Intended use for diagnosing rare diseases or meeting other local population needs.



- Creation of a comprehensive IDE process educational plan and implement requirements only after completion of this plan.

### **Verifying Accurate Leading-edge IVCT Development Act (the VALID Act)**

#### **CAP Support of the Verifying Accurate Leading-edge IVCT Development Act of 2023**

Should the FDA fail to modify the proposed rule to incorporate all the CAP's requested changes, Congress should pass legislation to regulate laboratory developed tests. Any legislation Congress passes should create a tiered risk-based structure for oversight of LDTs, include a targeted role for the FDA, and utilize whenever possible current laboratory reporting requirements. To that end, the CAP supports H.R. 2369, the VALID Act of 2023 ("VALID").

VALID reflects many of the policy priorities advocated by the CAP since 2009. It would establish a reasonable and balanced regulatory framework that would ensure quality laboratory testing for patients and minimize the regulatory burden on laboratories while allowing for continued innovation in laboratory testing. The CAP supports VALID's: (1) three-tiered risk-based system, which would focus the FDA's resources on high-risk tests, including high-risk LDTs, while leveraging existing structures to improve and promote patient safety; (2) "risk classification" framework, which is similar to one recommended by the CAP, and other groups; (3) use of mitigating measures for the further down-classification of test risk; and (4) overall regulatory framework.

Also, the CAP strongly supports the inclusion of guardrails in VALID that would prevent encroachment into CLIA-laboratory operations and infringement on the practice of medicine. The CAP appreciates the need for a premarket review process for high-risk tests defined in the legislation, and we appreciate the streamlined pathway that the technology certification provision provides for the development of new tests on existing technological platforms. The exempted categories laid out in the legislation, especially the grandfathering provision, are also appropriate. Further, the CAP is supportive of provisions that



clearly define test design and quality requirements, and the ability the legislation offers to modify existing LDTs to reduce burden and expedite patient care. Finally, the CAP continues to recommend that accreditors be allowed to submit documentation to the FDA on behalf of laboratories to further lessen the burden on laboratories.

### **CAP Opposition to CLIA “Modernization”**

Some organizations are pushing Congress to legislatively “modernize” CLIA and remove the FDA’s jurisdiction over LDTs and reassign jurisdiction to the CMS with a “CLIA-centric” approach. Most of the CLIA opening proposals, however, are extraneous to LDT oversight. In essence, their focus is not on ensuring the application and development of quality tests. In addition, previous administrations, as well as the current administration, have firmly held that oversight of LDTs should remain with the FDA due to the agency’s expertise in approving diagnostic tests for patients, some of which the CMS lacks. Further, as recently as January 2024, the FDA and CMS clearly delineated each agency’s authority and areas of expertise: the CMS regulates laboratories that perform patient testing, and the FDA oversees tests made outside of laboratories by manufacturers and LDTs developed and run within a single laboratory.

The CAP understands that rapid changes in technology and integration of the health care delivery system mean that many clinical laboratories are no longer just stand-alone sites. They have become an integral part of health systems, which often include at least one hospital and one group of physicians providing comprehensive care (including primary and specialty care) that connect with one another and the hospital through common ownership or joint management. These healthcare systems in a myriad of settings are using advances in technology to perform clinical laboratory testing at the point of care of patients. CLIA provides an adequate baseline to ensure the accuracy and reliability of clinical laboratory results, but the CAP recognizes that specific updates to CLIA are periodically needed to reflect and accommodate changes in practice and technology.





The CMS and the Centers for Disease Control and Prevention (CDC) have partnered to make targeted updates to CLIA, utilizing a regulatory approach, over the last several years. Much of this work is being initiated through the Clinical Laboratory Improvement Advisory Committee (CLIAC) to perform a comprehensive review of CLIA and identifying topics for potential changes. Thus far, CLIAC has identified the following areas that require updates. These include:

- Regulated Proficiency Testing (PT) Analytes,
- Revision of Personnel Regulations,
- Histocompatibility Regulations,
- Fees Under CLIA,
- Retention of Next Generation Sequencing (NGS) Data in Clinical and Public Health Laboratories, and
- Proficiency Testing Referral Alternative Sanctions for Certificate of Waiver Laboratories.

Moreover, the CMS and CDC may focus future modernization efforts on topics of *Histopathology, Cytology, Clinical Cytogenetics, NGS, and Biosafety*. The agencies recently released an RFI last summer that included *remote sign-out and histology laboratory regulations*. The CMS and CDC have also formed *CLIAC workgroups* to develop recommendations for new CLIA requirements for *NGS and biosafety*. The CAP firmly supports this targeted regulatory approach to updating the CLIA because it enables laboratories to continue providing services to patients without the major disruption CLIA-related congressional legislative intervention would cause.

### **Conclusion**

In conclusion, the CAP supports a legislative and regulatory framework for the oversight of LDTs that acknowledges the significant and important technological diagnostic advancements in medicine and the changing health care landscape. Legislative and regulatory activities in this space must ensure that



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patients continue to have access to high-quality, reliable, accurate, and innovative diagnostics. Again, the CAP appreciates the Committee's attention to these issues, and we look forward to working closely with all members of the Committee to ensure a balanced framework is adopted that prioritizes patient safety.

Thank you again for holding this hearing on LDT reform. The CAP looks forward to continuing to work with Congress and the FDA to find a flexible, commonsense policy that gives patients the highest quality laboratory tests.



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December 4, 2023

Robert Califf, M.D.

Commissioner

US Food and Drug Administration (FDA)

10903 New Hampshire Avenue

Silver Spring, MD 20993

Re: FDA Proposed Rule, "Medical Devices; Laboratory Developed Tests": Docket No. FDA-2023-N-2177

Submitted via Electronic Submission to [www.regulations.gov](http://www.regulations.gov)

Dear Dr. Califf:

The College of American Pathologists appreciates the opportunity to comment on the proposed rule entitled, "*Medical Devices; Laboratory Developed Tests (LDTs)*." As the world's largest organization of board-certified pathologists and leading provider of laboratory accreditation and proficiency testing programs, the CAP serves patients, pathologists, and the public by fostering and advocating excellence in the practice of pathology and laboratory medicine worldwide. As physicians specializing in the diagnosis of disease through laboratory methods, pathologists have a long track record of delivering high quality diagnostic services to patients and other physicians.

The CAP appreciates the agency's goal of addressing patient concerns and creating a framework to mitigate public safety issues with LDTs. Historically, LDTs have played a vital role in patient care and continue to represent some of the most innovative and in some cases the only tests of their kind offered to patients today. Since 2009, the CAP has advocated for a regulatory framework that enhances patient safety, maintains quality laboratory testing, and promotes innovation without creating significant regulatory burdens on pathologists and clinical laboratories. Moreover, the CAP proposed an LDT oversight framework that would use a stratified approach to effectively balance regulation by the FDA



and the Centers for Medicare & Medicaid Services (CMS) without stifling innovation or patient access to LDTs. The CAP's proposal focused FDA oversight on tests that currently have the least transparency and highest potential risk to patients. The CAP's proposal employed a three-tiered, stratified model that authorizes a role for third party accreditors and classifies tests based on their overall complexity and potential risk to patients based upon three categories: low, moderate, or high risk. In addition, analytic and clinical validation of LDTs would have a key role in any future LDT regulation.

The CAP has unique insights into the benefits and risks presented by LDTs and the many practical issues surrounding their regulation. As physician specialists in the diagnosis of disease, pathologists have a long history of delivering high-quality pathology and clinical laboratory services to patients. Pathologists therefore have a keen interest in ensuring that our ability to provide high-quality diagnostic services to our patients is not overly restricted. The CAP has significant concerns that the rule as proposed would lead to a large reduction in the number of highly accurate LDTs available in hospital and health system laboratories, which would directly result in a dramatic decrease in the availability of safe, effective, and in many cases innovative tests necessary for timely patient care.

While the CAP's comments should not be construed as approval or acceptance of the proposed rule, we offer the following specific comments in these areas.

- Requirements for Continued Enforcement Discretion
- Use of Existing FDA Regulatory Authority
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#### **Requirements for Continued Enforcement Discretion**

LDTs have been critical for the advancement of medicine and contributed to the evolution of modern scientifically based health care services. Today, LDTs continue to play a critical role in the advancement of medicine and clinical care for patients. Therefore, the CAP recommends the following categories continue under the FDA's enforcement discretion policies:

- Exempt tests offered prior to the rule's enactment;
- Forensic, Human Leukocyte Antigen (HLA), Manual tests;



- LDTs Developed and Offered Locally by a Clinical Laboratory;
- Adverse Events Reporting;
- Quality Systems (QS);
- Corrective Action and Removal; and,
- Labeling.

### **Exempt Tests Offered Prior to the Rule's Enactment**

The proposed rule seeks comments on LDTs that are offered as of the date of enactment, and that have not changed with respect to indications for use or performance after that date, to be allowed to continue under the agency's enforcement discretion policy. The CAP strongly recommends allowing tests that are performed and not changed with respect to the indications for use or performance to remain under enforcement discretion. Although there are currently many thousands of LDTs used in clinical care, most clinical laboratory tests performed today are low or moderate-risk and rely on packaged test systems produced by independent manufacturers and sold to laboratories. The large majority of LDTs are used "locally" within a hospital or health system and not marketed nationwide. In addition, there are mitigating factors to ensure these tests maintain adequate performance, such as the biennial Clinical Laboratory Improvement Amendments of 1988 (CLIA) inspection process, adjunctive testing, proficiency testing (PT) which is administered biannually in conjunction with the inspection process that can identify issues or problems within the testing processes, and close coordination of care with other clinicians. Lastly, the cost and time for clinical laboratories to submit data to the FDA would be excessive and overly burdensome given that laboratories are experiencing workforce shortages and financial challenges from decreasing reimbursement. Exempting tests currently offered also ensures continuity of care and a smoother transition, with adequate time for the agency to educate clinical laboratories on the regulatory requirements and processes such as risk classifications. There are specialty tests that have either no or too few FDA approved/cleared kits available to ensure continuity of care. The following are some examples:



- Toxicology confirmatory tests are almost entirely LDTs. FDA-approved toxicology tests are limited to screening tests that are subject to a high degree of cross reactivity resulting in false positive results and variable detection limits resulting in false negative results.
  - Opioids (oxycodone, hydrocodone, heroin, fentanyl, etc) - LDTs are needed for fentanyl analogs or other designer opioids.
  - Amphetamines (amphetamine, methamphetamine, MDMA/Ecstasy) - there are no FDA-approved options for designer amphetamines.
  - Emerging drug issues like xylazine or synthetic cannabinoids
  - Therapeutic Drug Monitoring (TDM) - LDTs are the only option for some newer medications to treat epilepsy and for antifungals. There is very little development of FDA-approved assays in this area.
- Hereditary genetic testing
- Molecular oncology testing: While FDA-approved platforms exist, our own data demonstrate that a significant number of laboratories modify FDA-approved platforms to include gene targets that have become standard of care but are not yet FDA-approved. The proposed rule cites an older, small and methodologically flawed study to suggest that the quality of molecular LDTs is poor (<https://doi.org/10.1093/ajcp/aqab164>). A recent, larger and more generalizable study demonstrates >90% accuracy for detection of both common and rare tumor-related mutations (<https://doi.org/10.5858/arpa.2023-0322-CP>).

***Recommendation: Allow for all LDTs offered prior to the rule's enactment to continue under FDA's enforcement discretion policy***

### **Forensics, Human Leukocyte Antigen (HLA), and Manual LDTs**

The rule proposes to allow some tests to remain under the enforcement discretion policy, including forensics, human leukocyte antigen (HLA) testing, and manual tests, as well as public health surveillance tests. The CAP supports continued enforcement discretion for these categories of tests; however, the CAP strongly disagrees with limiting continued enforcement discretion to only those



manual tests that do not use any automation. Pathologists analyze samples using advanced equipment and techniques to determine, diagnose, and inform treatment options. For manual techniques such as immunohistochemistry (IHC) and flow cytometry, pathologists use these tools to make diagnoses. For IHC, the automated staining process currently used in most laboratories has dramatically improved the consistency of stain quality and has helped streamline the pathologist's workflow and processes, thus allowing pathologists to have consistent access to high quality stains that ultimately improve patient care. In addition, for each case utilizing IHC, stain quality is assured as the pathologist reviews the stain controls in the context of each slide, thus verifying accurate stain performance before manually interpreting the findings and making the diagnosis. The same verification of controls and stain performance by the pathologist occurs with diagnostic flow cytometric analysis. Pathologists using these automated tools to gather information and manually make a diagnosis should meet the spirit of the FDA's enforcement discretion policy. Therefore, the CAP strongly recommends the FDA allow the use of automated techniques using components legally marketed for clinical use and interpreted by a pathologist to remain under the FDA enforcement discretion policy.

***Recommendation: Allow for the use of automated techniques using components legally marketed for clinical use and performed and manually interpreted by a pathologist to remain under the FDA enforcement discretion policy.***

#### **LDTs Developed and Offered Locally by A Clinical Laboratory**

The proposed rule is seeking guidance on a definition for academic medical centers (AMCs) and whether to apply general controls to academic medical center laboratories. We have heard concerns from our members outside of AMCs that providing an exemption to only AMCs would disadvantage them and impact their ability to provide appropriate and critical testing for their patients. AMCs provide important care to patients, as do community hospitals and regional health care delivery systems. An exemption should apply broadly to laboratories that develop LDTs in small volumes, using well-



characterized standard tests, to serve their local communities and intended for use in diagnosing rare diseases or to meet other local population needs.

To address patient care needs, LDTs are developed and validated for a myriad of reasons by the clinical laboratory that performs testing. Some of these reasons include the clinical laboratory modifying an existing cleared or approved manufactured packaged test system for the laboratory's patient populations (e.g. pediatrics), as modifications to these systems by manufacturers often never occur because the patient populations are too small or because appropriate FDA approved/cleared tests are not readily available in the marketplace. Another example of an essential test modification is the updating of antimicrobial susceptibility testing break points, which manufacturers often don't update on older instruments and which the FDA has recently recognized as an important patient safety issue. In addition, the clinical laboratory often develops LDTs to address emerging rare diseases, clinical needs raised by the local physician care team, or to ensure local communities have access to timely patient results for clinical decision-making (e.g. isolation of infectious patients). Dialogue between pathologists and other physicians within a local or regional health care delivery system allows for better understanding of the strengths and weaknesses of LDTs to address a clinically unmet need in a timely manner. Since medical practice undergoes continuous process change because of drug development and new treatments changing patient management strategies, the clinical laboratory must adapt and change in parallel to support or extend clinical practice. For these reasons, the locally offered LDT that is developed by the clinical laboratory actively involved in patient care serves as a mitigating factor for the LDT's risk since the LDT is used by pathologists and/or other physicians to confirm the diagnostic hypothesis. Therefore, the CAP recommends continued enforcement discretion for clinical laboratories developing low volumes of LDTs that are used for patients in their local community.

***Recommendation: Allow for continued enforcement discretion for clinical laboratories developing and running LDTs meeting the following criteria:***

- ***Offering LDTs in small volumes;***
- ***Serving their local communities with active involvement in patient care;***





- ***Using well-characterized standard tests; and***
- ***Intended use is for diagnosing rare diseases or meeting other local population needs.***

### **Adverse Events Reporting**

The rule proposes clinical laboratories submit a report to FDA if an adverse event occurs. Adverse reportable event (or reportable event) means:

- a. An event that user facilities become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury or
- b. An event that manufacturers or importers become aware of that reasonably suggests that one of their marketed devices:
  - i. May have caused or contributed to a death or serious injury, or
  - ii. Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The CAP supports adverse event reporting and requires clinical laboratories to have a voluntary reporting process in place to report such events to the FDA; however, very few clinical laboratories have had any reportable events. We anticipate that the FDA will need to implement a broad educational program to inform laboratory personnel on the adverse events process. This education will need to include a review of the FDA terminology, which is often different from that used in the CLIA regulatory process even when referring to similar criteria and standards. Therefore, we recommend adverse event reporting for clinical laboratories remain under the FDA's enforcement discretion policy until clinical laboratories understand reportable events and the process to comply with this requirement.

***Recommendation: Continued enforcement discretion for adverse event reporting until an educational program is undertaken.***

**Allow enforcement discretion for clinical laboratories using:**



- a. **New York State Department of Health Clinical Laboratory Evaluation Program (NYSDOH CLEP) or**
- b. **Veterans Health Administration (VHA).**

The proposed rule is seeking comments on whether it is appropriate to continue the general enforcement discretion approach, such that FDA generally would not enforce any applicable device requirements, where outside programs can be leveraged. The CAP supports the use of third-party reviewers such as NYSDOH and believes their review, and other programs with similar expertise and experience as the NYSDOH program, should remain under enforcement discretion.

***Recommendation: Allow continued enforcement discretion for clinical laboratories using NYSDOH or similar programs.***

#### **Quality Systems (QS)**

The rule is proposing to require clinical laboratories to comply with a subset of QS controls. These requirements include purchasing control, CAPA-corrective and preventive actions, records, and design controls. The CAP appreciates the FDA's proposing a subset of the QS for clinical laboratories, but we remain concerned about the duplicative nature of some of these requirements. QS were developed to define minimal quality system requirements that medical device manufacturers must implement to assure that the finished device will be safe and effective. As noted, there are close parallels with the CLIA requirements that are intended to assure the reliability and accuracy of laboratory results. While we acknowledge that differences exist between the two regulations, requiring laboratories to comply with a subset of QS would be duplicative, costly, and burdensome because laboratories would need to implement new processes and procedures as well as hire additional staff to comply. We support the agency's intent to ensure only quality components are included in the test development process and the practices are documented appropriately; however, our members remain concerned that the subset of QS elements are duplicative and potentially burdensome. We believe the FDA should re-evaluate its proposal on requiring the subset of QS, especially CAPA, purchase control, and records, or allow laboratories to adapt existing processes.



If the FDA elects to move forward with the subset of QS requirements, comprehensive information and educational sessions will be needed for laboratories to comply with the QS requirements. For example, when new CLIA requirements are implemented, the CAP conducts online inspector team leader and team member training. The CAP also conducts webinars, such as our Focus on Compliance webinar series, to educate laboratories on a periodic basis as to changes in compliance requirements. We believe the FDA will need to offer similar educational opportunities for laboratories to enable understanding and compliance. Also, more time will be needed for implementation by year three of the final rule. We recommend extending the compliance period for the subset of QS requirements, if required, and take the least burdensome approach to regulatory oversight.

***Recommendation: Allow clinical laboratories to remain under enforcement discretion and extend the implementation timeframe from year three until comprehensive QS education is implemented for clinical laboratories.***

### **Corrections and Removal**

Under existing regulatory authority, laboratories would need to provide reports of corrections and removals to FDA of any correction or removal of a medical device if the correction or removal was initiated to reduce a risk to health posed by the device or to remedy a violation of the act caused by the device which may present a risk to health. A report must be made even if the event was caused by user error.

The CAP is concerned about requiring laboratories to report corrective and removal instances as clinical laboratories are required under CLIA to document all corrective actions taken, including for test systems that do not meet the laboratory's verification and established performance specifications. The FDA requirement would require laboratories to create duplicative reporting processes to demonstrate that these corrective actions were taken. Since laboratories must comply with this requirement to obtain CLIA certification, the CAP recommends clinical laboratories remain under enforcement discretion if



they can provide documentation upon request of their corrective action and removal processes, as well as any actions taken.

***Recommendation: Allow laboratories to remain under enforcement discretion for correction and removal rules if they have documented processes, including any actions that have been taken.***

### **Registration/Listing**

The rule is proposing under existing FDA authority that clinical laboratories register with the FDA as manufacturers of LDTs and list details of the LDTs as it pertains to safety and efficacy, including conformity to safety standards. Clinical laboratories that develop LDTs would need to register and list with FDA, once they start developing, and at least once annually afterwards, to update their device listing. Registration must take place within 30 days of beginning to manufacture, produce, or assemble a medical device. The CAP has concerns about the potential regulatory burden for clinical laboratories to register and list with the agency and we anticipate some laboratories will view this requirement as too burdensome to offer testing and they may elect to stop providing important patient testing due to budgetary constraints this proposed regulation would cause. The CAP requires clinical laboratories as part of the accreditation process to have a list of LDTs that can be reviewed by inspectors. The CAP believes the registration and listing burden can be reduced by excluding low-risk tests from the notification process. Therefore, the CAP recommends allowing low-risk LDTs to remain under enforcement discretion if the clinical laboratory documents all low-risk LDTs performed.

***Recommendation: Allow for low-risk LDTs to continue under the enforcement discretion policy for registration and listing requirements.***

### **Labeling**

The rule is proposing that LDTs comply with the minimal device labeling requirements that provide instructions on intended and directions for use. The CAP is concerned that labeling requirements will add significant burden and cost for clinical laboratories to produce a label with, or in addition to, the clinical laboratory results. CLIA, in addition to other compliance requirements, provides limited space for clinical laboratories to add any additional elements to the report. In addition, electronic health records



(EHRs) would need to have data elements added that would require standardization and harmonization, which would add additional cost. The clinical laboratory currently offers similar information to the minimal device labeling requirements sought by the FDA in the clinical laboratory test ordering form or as part of the electronic order entry process. Therefore, the CAP recommends the FDA continue enforcement discretion for labeling requirements for LDTs if the clinical laboratory provides this information upon request.

***Recommendation: Allow clinical laboratories to continue under the enforcement discretion policy for general labeling requirements if the LDTs' information is documented and made available upon request.***

## **REGULATORY FRAMEWORK**

As the FDA is proposing to use its current regulatory authority to phase-out enforcement discretion for LDTs and use its existing regulatory framework, the CAP is very concerned about the impact the medical device regulations will have on a clinical laboratory's ability to continue to develop and perform LDTs. The existing regulations lack flexibility and do not meet the FDA's own least burdensome standard.

### **Risk Classification**

Under the agency's current regulatory authority, the agency has established generic types of devices and grouped them into medical subspecialties. Each generic device type is assigned into one of three regulatory requirements. The CAP has serious concerns about the existing FDA medical classification categories being used as it will subject many well-established and validated LDTs to higher-level regulatory requirements. These well-established LDTs represent the standard of care, with required proficiency testing and professional guidelines written for performance and interpretation.

Although some companion diagnostics have been down-classified to moderate-risk, the CAP estimates that at least several hundred LDTs would still be classified as equivalent to most existing companion diagnostics under the FDA's proposed rule and therefore classified as high-risk LDTs. The CAP remains



concerned that if the FDA rule is adopted without modification, it would subject many LDTs – which are well-established in medical practice and represent the standard of care – to the PMA process. The CAP believes that categorizing too many tests as high-risk LDTs, including well-established companion diagnostics, will harm patients by limiting access to testing or delaying testing results and increasing health care costs.

As with the QS, the FDA will need to provide comprehensive information and educational sessions for laboratories to determine test risk classification and how to comply. Clinical laboratories have limited resources to determine test risk in approximately 1,700 different generic types of devices and groups within sixteen medical specialties, so the agency will need to provide tools and resources to assist with this process. Given expected higher-level risk categorization and the complexity of risk determination, the CAP recommends the FDA conduct public panel meetings to discuss, educate, and determine appropriate risk classifications for LDTs.

***Recommendation:***

- ***Convene public hearings to determine test risk classification and solicit input on test classifications as an ongoing process to advise the FDA on these classifications.***
- ***Delay stages four and five until completion of a comprehensive educational campaign on the test risk classification requirements.***

**Humanitarian Device Program (i.e. Rare diseases)**

The Humanitarian Device Exemption (HDE) Program creates a regulatory pathway for products intended for rare diseases or conditions that affect small populations, namely a Humanitarian Use Device (HUD). An HUD is a medical device intended to benefit patients in treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals per year in the United States. There is a two-step process: (1) request HUD designation and (2) submit a HDE application. The HDE application is a marketing application that is like a premarket approval (PMA) application.



The CAP has serious concerns about applying the HUD program to LDTs due to its complexity and constraints. Clinical laboratories often develop LDTs for rare diseases that do not have existing approved/cleared test systems. While this program and Congress have offered incentives to obtain clearance, LDTs remain the only option for tests to serve the needs of many patient populations. Examples include PCR tests for vector-borne pathogens that are specific to certain areas of the country (e.g., *Anaplasma phagocytophilum*, Powassan virus, *Ehrlichia chaffeensis*, *Babesia microti*). Given that many of these tests are developed and run at the request of clinicians and do not have the volume to support commercial FDA approval, the CAP recommends these LDTs remain under enforcement discretion if they are serving their local communities, use well-characterized standard tests and are offered in small volumes.

***Recommendation: Apply general controls when LDTs are offered by special request to a laboratory from its local physician community and meet the following:***

- ***Offering LDTs in small volumes;***
- ***Serving their local communities and actively involved in patient care;***
- ***Using well-characterized standard tests; and***
- ***Intended use for diagnosing rare diseases or meeting other local population needs.***

#### **Investigational Device Exemption (IDE)**

The rule is proposing that any LDT used in conducting a clinical investigation to determine the safety and effectiveness of certain devices must be the subject of an approved investigational device exemption (IDE) before such investigation may commence. The IDE would apply to high-risk tests that use clinical data to support approvals. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. While exemptions are allowed for studies that do not pose physical harm or impact treatment decisions, which includes most clinical laboratory tests, the CAP is concerned about the impact this requirement will have on clinical laboratories using companion diagnostics and involved in clinical trials. We anticipate that the FDA will



need to implement a broad educational program to inform laboratory personnel on the IDE process. This education will need to include a review of the FDA terminology which is often different than that used in the CLIA regulatory process, even when referring to similar criteria and standards. The educational process will need to provide clarity around the IDE process and the applicability when involved with clinical trials versus other clinical studies.

***Recommendation: Create a comprehensive IDE process educational plan and implement requirements only after completion of this plan.***

**Summation**

In summary, the CAP believes this proposed rule to end enforcement discretion for all LDTs and use the existing FDA framework for the regulation of LDTs, as written, will severely stifle medical innovation, increase regulatory burden on clinical laboratories, introduce unsustainable costs as part of the development of LDTs by clinical laboratories, and in the end hinder the delivery of potentially life-saving testing to patients. For these reasons, the CAP does not support the proposed rule in its current form. Because of the complexity of the oversight of LDTs and the large number of problem areas in the proposed rule, as written, the CAP strongly recommends that the FDA provide more opportunities for public and stakeholder input before finalizing the rule and before implementation of the subsequent phases (e.g. phases 3 and 4).

We welcome the opportunity to discuss our concerns and recommendations with you. Please contact Helena Duncan, CAP Director, Scientific Regulatory Affairs and HIT Policy, at [hduncan@cap.org](mailto:hduncan@cap.org) if you have any questions on these comments.

Sincerely,

Donald Karcher, MD, FCAP

CAP President