



COLLEGE of AMERICAN PATHOLOGISTS

December 4, 2023

The Honorable 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

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

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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

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



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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 if you have any questions on these comments.

Sincerely,

Donald S. Karcher, MD, FCAP
CAP President