# Association of Pathology Chairs

**Promoting Excellence In Academic Pathology**

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December 1, 2023

Commissioner Robert Califf MD
Dockets Management Staff
Food and Drug Administration
5630 Fisher's Lane, Room 1061
Rockville, MD 20862

Re: Response to Docket No. FDA–2023–N–2177 for "Medical Devices; Laboratory Developed Tests."

Dear Commissioner Califf:

On behalf of the Association of Pathology Chairs (APC), we submit this letter as our formal response to the FDA's proposed rule (Docket #FDA-2023-N-2177) to regulate laboratory-developed tests (LDTs) like medical devices.

The APC is a non-profit organization which serves as the voice of academic departments of pathology and laboratory medicine in the U.S. and Canada. The APC represents the entire academic pathology leadership team of over 160 departments nationwide, whose academic clinical laboratories support the patient care mission of their academic health systems, in addition to the research and education missions of their medical schools. The APC enables our members and their departments to meet unique needs in the dynamic and often challenging academic health care environment. Notably, the academic environment in which our members practice, innovate and lead is not a manufacturing environment. Our members practice pathology and laboratory medicine within academic health care systems and are integrated into clinical decision-making with their fellow providers; as academic pathologists, they bear direct responsibility for patient care and outcomes, similar to other academic physicians, thus ensuring safety and effectiveness.

The APC's comments and recommendations regarding the proposed rule are outlined below:

## I. General comments and concerns

A. The APC recognizes that current regulations as defined in CLIA 88 need updating and do not adequately address all facets of safety, particularly regarding LDTs.

B. The APC commends the FDA for their commitment to patient safety and their interest in the laboratory's critical role in safe patient care via safe clinical laboratory testing.

   i. Safety is number one among the six domains of health care quality, as listed and defined in the National Academy of Medicine (NAM)'s landmark report in 2001 *Crossing the Quality Chasm: A New Health System for the 21st Century* (1).

   ii. The APC recognizes safety as a core value of the specialty of pathology. A strong culture of safety and continuous quality improvement is fundamental to the practice of academic pathologists and other clinical laboratorians. This culture engenders trust among those we educate in our medical schools and residency programs and creates confidence in our laboratory services among providers and patients, many of whom travel significant distances for unique diagnostic testing and care that only an academic health center can provide.

C. There is a risk for substantial potential harm to patients, since five of six quality domains defined by NAM are not addressed in the FDA's proposed rule. We have serious concerns that there will be a lower quality of laboratory services for patients based on findings from a recent survey of APC members (see details below). Predicted impact on each of the other quality domains are described below; note that definitions of each domain are included below for clarity, along with available supporting evidence.

   i. Effectiveness (i.e., services based on scientific knowledge; Quality domain #2):

      1. The FDA's proposed rule is not based on a body of scientific knowledge or evidence, as expected within the quality domain for effectiveness. Instead, this rule appears to be prompted largely by the concerning anecdotes included in the document. These examples are not well-characterized and are mostly irrelevant to the circumstances in academic clinical labs.

      2. The proposed rule includes several requests for data as part of submitted responses, indicating the FDA's recognition of this gap. A recommendation for a comprehensive national data gathering project for evidence-based decision-making to support regulatory oversight is included in our Recommendations section below. Great care should be taken to develop an irrefutable base of evidence for the costly, disruptive, unprecedented changes proposed by the FDA, before any final rule is implemented.

      3. To fill the current information gap and provide guidance for our recommendations, **the APC conducted a confidential online survey** among its members in the short time available. The findings provide a unique window into academic clinical laboratories and form the basis for our quality concerns outlined in the bullets immediately below, as well as for our recommendations which follow.

         a. The survey was distributed to APC members via the APC list-serve and consisted of 27 multiple choice questions and opportunities to provide written comments.

b. Responses were received from 39 APC member laboratories and included 18 of the 45 states with allopathic medical schools plus the District of Columbia.
c. All respondents described themselves as high-complexity labs. 95% (37/39) reported that they were academic medical center laboratories. 86% of the respondents reported having multiple CLIA licenses for their laboratories, chiefly ranging from 8-25 with one reporting 88 CLIA licenses. 46% report clinical revenue of $100,000,000 or more.
d. 42% (16/39) of the survey respondents described themselves as a local reference lab, 32% (12/39) as a regional reference lab, and 8% (3/39) as a national reference lab. None of the respondents described themselves as a commercial laboratory.
e. None of the laboratories reported being a "research use only" manufacturer, "analyte-specific reagent" manufacturer, or an "in-vitro diagnostic" manufacturer.
f. A wide range of LDTs were offered among the respondents (see figure in Appendix). Only 39% (15/39) of respondents reported less than 50 LDTs on their test menu. 43% (17/39) reported 200+ LDTs on their menu with 5 labs reporting 400+. 69% reported that LDTs were 20% or less of their test menu. 83% reported that LDTs were less than 20% of the overall tests performed internally in their laboratories. 46% reported that 30% or less of their LDTs were "high-risk".

ii. Efficiency (i.e., avoiding waste, including waste of equipment, supplies, ideas and energy; Quality domain #3):
1. Validation via an FDA trial is a time-consuming, expensive, labor-intensive, lengthy, and inefficient process, as described in a recent publication from UCLA (2). The large number of LDTs on the menu of academic clinical laboratories -- which chiefly run in the hundreds per the APC survey -- would make the requirements in the FDA's proposed rule a large, onerous and difficult task for academic clinical laboratories. A recent published report from the University of Utah's ARUP laboratory illustrates the large number of LDTs that a single laboratory would need to address (3).
2. Most academic clinical laboratories currently have insufficient resources to efficiently meet the FDA's timeline:
a. The current laboratory workforce is insufficient to conduct the work necessary to fulfill the requirements by the FDA's proposed rule. The APC survey demonstrated that 100% of the respondents have staffing shortages. This is echoed in the substantial vacancy rates in US clinical laboratories reported in the American Society of Clinical Pathology's recently published vacancy survey (4). Vacancy rates range from 7-19% in all the laboratory's sections. Sectors with many LDTs, such as hematology/coagulation and chemistry/toxicology have some of the highest vacancy rates at 17% each (4).
b. Insufficient space to conduct the work required by the FDA proposed rule is reported by 77% (30/39) of respondents to the APC survey.

c. There is insufficient knowledge and experience for this monumental task among academic clinical laboratories. Slightly more than half (54%, 21/39) of APC survey respondents report experience conducting an FDA trial and only 23% (9/39) report experience with pre-market approval, and 15% (6/39) have experience with a 510(k) or de novo application, per the APC survey.

d. Financial resources to support work associated with the FDA proposed rule are uncertain. 62% (24/39) of respondents in the APC survey said they did not know where they would get financial support so that they could meet the mandates in the FDA proposed rule. 44% (17/39) of respondents anticipated getting resources from their hospital/health system. Thirteen percent (5/39) anticipated getting resources from the school of medicine and an equal percentage indicated that this would need to be absorbed into the department budget. 90% (35/39) anticipated that they would likely receive fewer institutional resources for clinical activities or the laboratory as a result of this new expense, and 79% (31/39) anticipated fewer resources for education or research available due to funding this work.

iii. Timeliness (i.e., reducing waits and harmful delays for both those who receive and give care; Quality domain #4):

1. The FDA's proposed timeline is unrealistic since the requirements for FDA approval cannot be conducted in a timely fashion due to the large number of LDTs and insufficient resources, as illustrated by the APC survey findings above. The FDA review process is also lengthy once data is submitted. Only 1 of the 39 respondents in the APC survey reported that they were likely able to implement the requirements of the FDA proposed rule within the 4-year timeframe.
2. 97% (37/39) of APC survey respondents anticipate delays in providing test results consequent to implementation of the FDA proposed rule.
3. A cascade of events with associated delays will occur that will adversely impact patient care. This is largely due to contraction of hospital laboratory test menus during the FDA validation and approval process and later when laboratories cannot meet the FDA's timeline in the proposed rule. 95% (37/39) APC survey respondents report that more outsourcing of tests will be necessary. Outsourcing has inevitable consequent delays in receiving test results; this assumes that a similar FDA-approved test is even available elsewhere. Result delays then lead to delays in patient communication, treatment planning, and initiation of treatment. All these delays can lead to increased morbidity and possibly even mortality.

iv. Patient-centeredness (i.e., care that is respectful of and responsive to individual patient preferences, needs, and values; Quality domain #5): Seriously ill and vulnerable populations with serious illnesses may not get the testing they need or want if LDTs are removed from the menu -- or patients may get inferior alternatives.

1. 90% (35/39) of labs predicted that some LDTs will be indefinitely removed from their test menus until commercial options become available. Temporary removal of LDTs from the test menu was predicted by 72% (28/39) of respondents while an FDA trial is conducted. 51% (20/39) predicted that fewer new FDA-approved tests would be implemented due to deployment of lab staff toward LDT validation.
2. Cancer and transplant care was the most frequent clinical scenario for ordering LDTs at University of Utah's ARUP laboratory. This includes tests for viruses in immunocompromised individuals or to diagnose and monitor hematopoietic neoplasms (3). Most of these tests are not available commercially, so there would be no alternatives if FDA approval was not achieved.
3. The pediatric population will be seriously impacted since modifications of almost ALL (if not all) tests that are FDA-approved for adults would require approval of modifications to LDTs for use in children.
4. If LDTs cannot be FDA-approved within the given timeframe, removing them from the test menu will create anxiety, distress, delay, and dissatisfaction for already stressed patients. Published studies demonstrate that timely test result communication is important to decreasing patient anxiety (5, 6)
5. Innovation to develop new and better tests to improve patient care will be slowed or even halted due to the major barriers imposed by the FDA and resources diverted to the FDA approval process. 92% (36/39) of APC survey respondents reported that there will be less innovation to create and offer new tests to improve patient care due to the FDA's proposed rule.

v. Equity (care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status; Quality domain #6):

1. Academic health systems are disproportionately represented in health care for vulnerable populations and, as indicated by APC's survey, access to these and other patients will be impacted. 74% of respondents predicted less access for uninsured and underinsured patients. 64% (25/39) of respondents predicted less general access to lab services due to decreased laboratory capacity since resources would be diverted to the FDA approval process. The FDA's proposal represents an unfunded mandate whose excessive costs must be absorbed by hospitals and health systems, and ultimately passed on to patients as higher costs and/or by limitations of patient access. Since most academic health systems function as "safety net" hospitals, the financial impact on access will have a substantial effect on the underinsured or uninsured, i.e. our nation's most vulnerable members.
2. Patients with rare diseases will be disproportionately affected, since LDTs are typically created in the academic clinical laboratory to support the unmet clinical needs of patients who seek care at an academic health system. Commercial alternatives are typically not developed due to low volume of testing and little opportunity for profit.

D. Other comments on laboratory quality

vi. Overall quality of LDTs would not improve with the FDA's proposed rule:

1. None of the respondents in the APC survey anticipated a decrease in diagnostic errors or adverse events if the FDA's proposed rule was implemented, nor did they predict that adverse events would create more trust from patients or improved access for underinsured or uninsured patients.
2. 100% of APC respondents investigate and report any LDT errors thorough the laboratory's usual quality process, including use of the incident reporting system.
3. Survey respondents note that they do try to replace an LDT if an FDA-approved test becomes available; however, more than two-thirds of the respondents said they have never replaced an LDT.
4. Personal accountability is a key part of the quality program and an essential element of professionalism for pathologists and laboratory staff, and central to ensuring patient safety. Since the medical director's name is on the report for all types of testing, an inaccurate result could cause the director to lose their medical license. This illustrates the medical director's commitment to quality and their personal connection to every patient.

E. The current 60-day response period is insufficient for adequate data-gathering to fully illustrate and examine these complex issues. Extension of the review period is a necessity and would facilitate evidence-based regulations. National data is currently non-existent regarding the universe of LDTs, LDT volumes and practices, safety issues, and financial and patient-care impact of various LDT regulatory scenarios. Proposed regulations appear to be based chiefly on anecdotes and small series.

## II. Recommendations from APC:

A. Extension of the comment period to 180 days (and preferably for 9-12 months): This request aligns with the Federal Register's *Guide to the Rulemaking Process* which notes that "…for more complex rulemaking, agencies may provide for longer time periods, such as 180 days or more." The issues are clearly too complex to adequately address within the standard 60-day period, and deserve more time for data-gathering and thoughtful analysis.

B. Data collection via a national LDT "landscape" project should be conducted during this extended period to illuminate practice and resources and inform development of regulatory guidelines, implementation, and oversight.
   i. National data collection on LDT practices aligns with the FDA's request for data and their desire for evidence-based policies as stated in the proposed rule.
   ii. Regulatory scenarios should be created and evaluated in the context of data as part of this landscape project and should include:
      1. A risk-based regulatory process should be evaluated. This would include regulation of tests deemed as "high-risk" via the pre-market approval process. The APC shares the FDA's concern regarding the safety of some commercial LDTs which we deem as high-risk, including:
         a. Those with "black box" algorithms.
         b. Companion diagnostics and other tests intended for treatment decisions which do not include interpretation by a pathologist.

c. LDT kits or AI-based systems that are sold directly to consumers or to patients for their at-home use.

2. "New" regulatory models/scenarios should be evaluated in the context of data, including:
    a. Models based on the state of New York's Department of Health laboratory regulations for LDTs.
    b. Developing potential "extenders" to the FDA for regulatory review and approval of LDTs, such as deemed "accuracy centers" suggested by Mass General Brigham in their submitted response to the proposed rule. Alternatives could alleviate potential bottlenecks for approval processes.
3. Sustainability and financial impact of different scenarios/models should be evaluated, including impact to laboratories and health systems to implement the proposed rule, as well as implementation costs to the FDA or other oversight agencies.

iii. An outside entity should lead data collection to ensure trust by all stakeholders.
1. A government agency, such as the GAO, or an outside organization chosen via a competitive contract are potential options for project leaders.
2. A successful example of a previous landscape project resulting in formal recommendations and best practices is the 2012 cooperative agreement awarded by the CDC to the College of American Pathologists (CAP) to conduct a national survey of quality assurance practices in gynecologic cytology (7). The project's workgroups used the data to define best practices for laboratory quality. CAP, as the awardee, used a collaborative process that involved other pertinent professional organizations to develop a survey which was sent to 1250+ CLIA-certified cytopathology laboratories. Over 750 responses were received creating an unparalleled window into cytopathology practices. This survey data, along with published evidence from the literature and the lived experience of the practitioners participating in the workgroups, allowed creation of evidence-based guidelines which continue as the gold standard today. A similar process should be employed to create evidence that can be used in regulations to address LDT concerns.
3. Collaborative participation by practicing pathologists and other laboratory professionals to analyze data, develop regulatory guidelines and timelines for implementation with FDA and the Center for Medicare and Medicaid Services (CMS) is recommended and will enable achievable regulations that fit within the boundaries and challenges of real-world laboratory practice. This will also facilitate buy-in and acceptance of new or revised regulations since laboratory professionals will feel represented and heard.

C. <u>Initiate the long-overdue update to the Clinical Laboratory Improvement Act (CLIA) to complement and enhance an FDA oversight process</u>: The APC supports the CLIA modernization framework recently submitted by the Association for Molecular Pathology. Enhancing and modernizing CLIA will strengthen and close gaps in

regulatory processes. Oversight by CLIA and the related laboratory accreditation by CMS should continue under these updates and does not necessarily preclude additional oversight by the FDA, especially for direct-to-consumer and commercialized products.

D. <u>If an academic "carve-out" is included (which we do not support), modify the definition of "academic medical laboratory":</u>
    i. Remove the requirement for "same physical location" since this does not reflect the realities of academic laboratory location.
        1. Many academic clinical laboratories are split into multiple locations. Often only the "core laboratory" is co-located on the same campus as patient care services since rapid results are necessary for surgical, emergency, and ICU care. Other laboratory sections may be off-site to achieve larger and more affordable space, and to be more centrally located for the academic health system's community network.
        2. Academic clinical laboratories frequently perform testing at a central site for integrated care of outpatients seen at the academic health system's network of community clinics. For efficiency, samples are brought by courier from the distant clinics sites to the central laboratory location(s) which may not be co-located with any patient care services.
    ii. Remove the requirement of a "residency or fellowship related to test development": We appreciate the FDA's worthy consideration of house staff education, particularly future pathologists; however, the absence of a pathology and/or laboratory medicine residency or fellowship program should not preclude designation as an academic clinical laboratory. Even without a training program, the laboratory may still be owned and operated by an academic health system to provide integrated services that support care provided by academic physicians to patients within their network.
    iii. AAMC's July 2022 definition of an academic clinical laboratory is preferred since it includes the following key characteristics:
        1. The academic clinical laboratory is an integrated and integral aspect of an academic institution, which provides direct patient medical care.
        2. The primary role of the lab is to provide testing and interpretation for the benefit of the patients and clinicians in an affiliated hospital or academic health center as a part of the treatment decision-making process.
        3. The academic clinical laboratory has been certified by the Centers for Medicare & Medicaid Services through the CLIA (Clinical laboratory Improvement Amendments) program to conduct high-complexity tests.

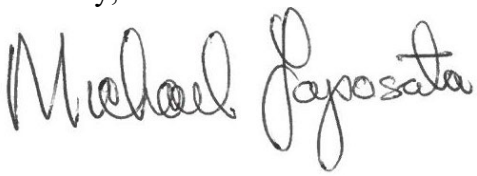
E. <u>Deadline for full implementation should be extended from 4 years to at least 8 years.</u> Given the hundreds of LDTs in each laboratory and the labor-intensive and time-consuming process for FDA trials, it will take many years to achieve FDA approval for a laboratory's LDTs.

In summary, as we note above, the FDA's proposed rule has noble intent, but raises substantial concerns, particularly regarding anticipated adverse effects on many of the domains of quality. We feel certain, based on evidence from our survey, that there is strong potential for patient harm due to lower quality of laboratory services and by extension, lower quality of health care provided by all specialties. The APC is therefore emphatic in our recommendation that the FDA does not move forward with their proposed rule as written.

To shape appropriate regulation of LDTs, we strongly recommend extension of the review period to allow a comprehensive data-gathering process to more fully illuminate LDT laboratory practices and related issues. This process should involve collaboration with experienced pathologists and laboratory professionals and take into account the cost and consequences of potential regulatory scenarios. This evidence can then be used to create safe, appropriate, and achievable regulations and best practices for LDTs. The evaluation process should include evaluating recommendations for long-overdue updates to CLIA that better address LDT practices, and for accreditation of laboratories by CLIA.

We appreciate this opportunity to comment and look forward to providing additional information and working collaboratively with FDA, CMS, and others to achieve our mutual goal of high-quality evidence-based laboratory services and contemporary regulations that ensure excellence in all domains of health care quality, including safety.

Sincerely,



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APPENDIX: