Association of Pathology Chairs

Promoting Excellence In Academic Pathology

100 West 10th Street, Suite 603, Wilmington, DE 19801
Tel: 302-660-4940 Email: info@apcprods.org Web: www.apcprods.org

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The Honorable William M. Cassidy, MD
Ranking Member of the Senate Health, Education,
Labor and Pensions Committee

Email: diagnostics@help.senate.gov

RE: Response to Questions on FDA & CLIA Regulatory Frameworks for Diagnostics

Dear Senator Cassidy:

The Association of Pathology Chairs (APC) greatly appreciates the opportunity to share our responses to your questions regarding practices related to laboratory developed tests (LDTs).

The APC is a non-profit organization which represents 160 academic depts of pathology and laboratory medicine in the U.S. (plus others in Canada) and empowers the entire leadership team (not just chairs) in the delivery of the tripartite academic mission: Research/innovation, Education, Patient care. Pertinent to the clinical mission and your questions, our members are responsible for patient care and clinical innovation within hundreds of clinical laboratories directed by faculty in academic departments of pathology and laboratory medicine at their academic medical centers. The APC supports members and their depts to meet ever-changing challenges in academic medicine through education, leadership training, data gathering and sharing, networking and advocacy.

Please note that members of the APC are NOT manufacturers of tests, devices, kits and DO NOT work in a manufacturing environment – the usual jurisdiction of FDA. Our academic faculty, including pathologists and PhD clinical laboratory scientists, are directly responsible for the quality of laboratory tests performed within laboratories associated with their academic medical centers. These centers serve the nation's sickest, most complex, and often most vulnerable patients, especially children, cancer patients, transplant patients, and those with rare diseases.

Our responses to your questions are below.

FDA Regulatory Framework for Diagnostics

How well is FDA's medical device framework working for the regulation of diagnostic products? Are there improvements that should be made? Of these specific changes, which would require Congressional action, and which can be effectuated by FDA alone?

Industry-developed devices and kits:

- Many academic medical centers involved with the in-vitro device (IVD) industry and various commercial submissions via the FDA's current processes (510k, PMA, and de novo submissions) have found that the FDA has not

always been consistent, expeditious, or pragmatic. A recent publication by Caldera J et al provides an excellent illustrative example of UCLA's costly, onerous, and time-consuming experience pursuing validation for FDA approval of monkeypox testing (https://www.sciencedirect.com/science/article/pii/S1386653223002342).

- FDA regulators are not always subject matter experts, and approvals are unduly driven by biostaticians, who are knowledgeable about statistics, but often far removed from clinical practice. For example, high sensitivity cardiac troponins, despite being in routine use outside the United States with significant clinical evidence showing benefit, took over nine years to get FDA approval. FDA should have more pragmatic approaches in approving IVDs. Examples of issues include:
- The FDA should have more pragmatic approaches in approving IVDs. Examples of issues include:
    - Approval process of devices of the same type, testing method, and disease category is variable and inconsistent. One company can get approval for their device/method, yet another company with an identical device/method who follows the same submission process may not get approved and is required to do further work, incur additional costs, and in some cases never receive approval.
    - FDA tends to avoid providing the specific guidance that test developers need to create successful submissions. As an example, the definition of "critically ill patients" is not defined by FDA, yet FDA requires manufacturers to develop devices (e.g., glucose meters) for this population.

Laboratory-developed tests (LDTs):

- Much of the testing performed in labs are not devices or kits, though these may be used. Lab testing is generally a process, and includes critical steps both before and after the use of the test kit. These all must be performed correctly and are reviewed and assessed as part of the CLIA oversight process which is key to overall quality in medical laboratories.
- Likewise, LDTs are neither devices nor test kits, and therefore do not and should not fall under the purview of the FDA. LDTs are internal laboratory processes and procedures designed chiefly to address the needs of patients and providers served by that laboratory.
- Not only is the FDA's proposed rule inappropriate re: their authority, the FDA lacks data on how many LDTs are subject to their proposed rule (including both de novo LDTs and those that represent FDA approved kits that have been modified to meet the specific needs of a particular clinical environment). A recent survey by APC indicated that most academic clinical labs have hundreds of LDTs. The onerous submission requirements and lengthy FDA review process would prompt removal of LDTs from test menus, either temporarily during FDA validation and submission, or permanently if laboratories lack the resources to pursue FDA approvals. Many tests are performed in the acute care setting because timely results and local expertise are required to appropriately care for complex patients; removal of these tests to distant reference laboratories would significantly degrade the quality of care. Further, innovative tests are often developed in academic laboratories to suit the specific local needs of their patients and programs; the FDA proposed rule would compromise such innovation.

Does the current device regulatory framework support the review of diagnostics that are developed using AI or that incorporate AI?

The current framework does not adequately support review of diagnostics that are developed or include AI. Two different scenarios for use of AI should be considered and reviewed accordingly:

- AI tools that replace a physician: The FDA should identify and involve more AI subject matter experts, and also raise the bar for FDA regulator knowledge. This will be critical to the review and approval of AI platforms in a timely fashion, as well as for the production of quality applications for patient care. The academic pathology community is concerned that the FDA may not have sufficiently appropriate experts that can field questions or review AI platforms that replace a physician or have no

human physician review. This is an emerging field, and like many new medical technologies, some less than optimal platforms may still make it through the process. AI experts in many industries are stating that they themselves don't know the capabilities of AI (e.g., Open AI, Tesla, etc.), especially generative AI. It is therefore unrealistic for the public or the profession to expect FDA regulators to have perfect knowledge.

- AI tools that assist a physician:
  - Assistive AI applications already exist in digital pathology and cytology, and are emerging for genomic analysis and predictive analytics for a variety of conditions using a wide range of information from the medical record. Digital cytology systems for AI-assisted screening Pap tests are an example and have received FDA-approval as a medical device. In this context, an AI tool should be regulated under the FDA's medical device regulatory framework, like other tools used for the practice of medicine.
  - For laboratory developed tests utilizing local proprietary AI algorithms, oversight by CLIA to ensure analytic and clinical validation would be appropriate. We support the CLIA Modernization Proposal submitted by the Association for Molecular Pathology (AMP) (https://www.amp.org/AMP/assets/File/advocacy/Amendments%20to%20CLIA%20modernization%20legislative%20text%2011_7_23%20FINAL.pdf?pass=70, page 7).

What, if anything, makes diagnostics distinct among FDA-regulated medical products to warrant specific attention to how AI may be used in the review of product submissions?

AI is only as good as the data it was trained on, and patient care is dynamic; therefore, the data used for training to drive improvements in AI and will be key to its appropriate and safe evolution. It is very important to note that the era of generative AI is moving rapidly. FDA is notoriously slow, and by the time an AI device is approved, the method may be obsolete.

Are the regulatory pathways intended to evaluate diagnostics for special populations (i.e. rare diseases or genetic disorders) working? How could they be enhanced to accelerate and authorize products for special populations, for example, certain companion diagnostics for rare biomarkers?

The FDA process is too expensive and cumbersome for diagnostic tests for many special populations, including rare diseases. There are times when FDA makes near-impossible demands, including requiring sample types that are extremely challenging to obtain in rare diseases or children, of the FDA asks for biomarker concentrations that are rarely encountered in clinical practice. Because of these demands, test manufacturers tend to develop and seek approval for kits which will yield a sufficient market and profit to cover the development costs. Tests for rare diseases don't have such a market. To fill this void, hospital laboratories often develop tests for rare diseases in order to adequately serve their patients. Notably, many of the commercial kits in use today were developed based upon years (decades) of successful diagnosis using LDTs, which demonstrated the need for broader availability of many tests (for example, herpes simplex virus PCR on cerebrospinal fluid, rather than a brain biopsy to diagnose infections).

How could they be enhanced to accelerate and authorize products for special populations, for example, certain companion diagnostics for rare biomarkers?

As mentioned above, validation materials for rare diseases and new diseases can be very difficult to obtain; increased flexibility is needed. The upcoming FDA regulations for LDT will hinder this greatly. FDA should allow means to better use "real world data."

Are there regulatory hurdles to expanding the settings in which diagnostics are performed, i.e. point-of-care (POC) tests performed in patients' homes?

Home testing, direct to consumer testing (DTC), and devices such as continuous glucose monitoring (CGM) require strict regulation and are ideal for FDA oversight. These can potentially yield inaccurate results, since there is little control over the environment in which the device or kit is being used, and the person performing the test. In contrast, testing done in CLIA accredited high-complexity laboratories occurs in well-controlled environments that include performance by trained and certified personnel following strict procedures:

- CGM does not fall under CLIA, but the testing methodology is exactly the same as blood glucose monitoring systems which are FDA approved and carry the same limitations as blood glucose monitoring systems. Accordingly, CGM should fall under CLIA.
- Likewise, home testing, DTC, and all forms of point of care testing, especially waived devices, should be held to higher standards.

What are your views on FDA's implementation of predetermined change control plans; is FDA's approach in its recent guidance readily applicable to IVDs and other diagnostic products?

PCCP does not appear to be appropriate for LDTs in academic medical laboratories, and seems most applicable to manufacturers, especially in AI/ML, who can perhaps better predict and pre-specify intended modifications and methods/implementation to avoid additional premarket submissions.

In what ways could/should FDA leverage regulatory flexibilities to reduce testing barriers?

Allow LDTs to be deployed by academic and hospital laboratories. This real-world data provides a more cost-effective approach than the current process. LDTs allow these labs to generate the key data that would facilitate more formal FDA submissions.

Does FDA's current risk classification framework properly measure risk versus regulatory controls for diagnostics products?

No, all diagnostics that result in management decisions are potentially high risk. Indeed, the companion diagnostics guiding treatment decisions might be viewed as lower risk than tests employed for diagnosing and classifying cancers.

If not, how can FDA's risk-based regulatory approach to diagnostics be improved to better align the degree of regulatory oversight with patient risk and benefit?

The FDA needs to employ bona fide scientific and clinical experts and needs to update rules and regulations.

In considering reforms to FDA's risk classification framework for diagnostics, what types of IVDs should be exempt from premarket review?
What factors related to risk management should be applied to risk classification of IVDs?

PMA exemption should be awarded to tests that address time sensitive, high-risk diseases or novel applications where no existing test is available.

Is the "safety and effectiveness" standard against which diagnostics are reviewed the most appropriate review standard to assign risk management for clinical tests?

Generally, this is appropriate, but the standards may be inconsistent for manufacturers (and therefore possibly for academic and other laboratories in the future). Likewise, standards may be misguided, since the real-world situation is not always familiar or apparent to reviewers. As mentioned above, high-sensitivity troponin is an excellent example. This test has been in use since 2009 in Europe with abundant data showing benefit to patients. The FDA took 9 years to approve this test, and the final issues were related to the term "high

sensitivity". Europe and Asia use this terminology. The FDA ultimately required the manufacturer of this first-approved test to call it "Gen 5" Troponin T. This created significant confusion for clinicians, and later other manufacturers were allowed to call their assay "high sensitivity". This illustrates both the short-sightedness and inconsistencies of the FDA reviews.

In addition, there are some issues with requirements for effectiveness: Predefinition of performance targets (detectable viral numbers) varied by orders of magnitude among the RT-PCR assays the FDA approved for COVID detection, rendering some of these assays totally worthless.

CLIA Regulatory Framework for LDTs

Do the proposed reforms to FDA's device framework warrant the establishment of a new regulatory pathway specific to diagnostics? If yes, what are the principles that should guide such a new framework, as it would be applied to diagnostics currently subject to FDA premarket review?

The current framework appears to be appropriate, but clearer standards are needed on the risks of non-high complexity personnel performing LDTs. State laws and federal laws may be inconsistent here. In CA, for example, regulations appropriately require that high complexity testing (including LDTs) are effectively clinical laboratory scientists/medical laboratory scientists), with oversight by those boarded in anatomic and/or clinical pathology or as high-complexity clinical laboratory directors.

What updates to the clinical laboratory regulatory structure under CLIA should Congress consider to reflect the latest scientific practices and safety standards?

Oversight by CLIA of laboratories and their LDTs (aka laboratory-developed procedures) has served patients, ordering providers, and laboratories very well. This is well-described in a recent publication with multi-institutional authors describing the benefits of CLIA oversight with many illustrative LDT examples. (*Acad Pathol* 2017 Jul 16:4:2374289517708309. doi: 10.1177/2374289517708309)

To ensure evidence-based oversight that reflects the latest scientific practices and safety standards, there needs to be full consideration of contemporary practice (including challenges), and emerging trends. The APC has therefore recommended a national landscape project examining laboratory practices that would include data-gathering, and development and testing of various regulatory scenarios, financial impact, and feasibility. This was included in our written response to the FDA regarding its proposed rule. Important areas to be addressed include molecular diagnostics, the role of biostatisticians, and computational approaches, including AI/ML.

Reform should also include more evidence-based and faster processes to approve quickly emerging tests. CLIA already requires laboratories to assess the analytical validity (precision, accuracy, analytical sensitivity, and analytical specificity) of laboratory tests. Many laboratories also provide documentation of clinical validity as well by providing peer-reviewed literature or textbook or clinical validation studies performed in the laboratory (CAP All Common Checklist-COM.40640. 8.24.2023.)

What are your views on the effectiveness and use of the Clinical Laboratory Improvement Advisory Committee (CLIAC) in providing scientific and technical guidance to inform potential updates to CLIA standards?

CLIAC is a helpful, effective, and forward-thinking group that gathers multi-disciplinary and multi-stakeholder data to craft the best solutions. It is a very slow process and could benefit from updates and new processes.

Do the proficiency testing programs currently approved by the Department of Health and Human Services (HHS) reflect the latest clinical standards of laboratory medicine? Are there specialties, subspecialties, or analytes that should receive greater consideration for HHS approval?

Many, but not all currently approved proficiency testing (PT) programs reflect the latest clinical standards. For the majority of tests, PT programs provide detailed information to testing labs about relevant analytical issues, including kit, method and instrument variations. One problematic area to be considered is that the PT challenges are unable to adequately reproduce real-life practice, leading to some misleading or nonsensical results. There are situations where PT material manufacturers produce materials that are contrived to achieve certain target levels, but do not resemble clinical samples closely enough to meaningfully assure proficiency for testing actual patient specimens.

How well does the existing enforcement structure under CLIA work in ensuring compliance with regulatory requirements and taking action against noncompliance? What should be improved, if anything at all?

The existing enforcement structure under CLIA works well, as demonstrated by Theranos: it was the CLIA review process that identified issues and imposed penalties that ultimately shuttered the laboratory.

Should legislative reforms address CLIA's quality system requirements? If yes, which of those changes would require Congressional action, and which could be effectuated by CMS alone?

CLIA's quality system requirements are largely fine in their current form. Increasing the frequency and availability of PT materials would helpful.

Where does redundancy exist, if at all, within the current CLIA regulatory structure with respect accreditation standards under federal and state licensure programs, as well as through CMS-approved accreditation organizations?

There is good coordination between CLIA and state departments of public health (including the excellent New York state example) as well as other CMS-deemed status organizations.

In considering legislative reforms to CLIA, should LDTs be defined in statute? What aspects of test development would characterize such a definition?

We support the definition provided by Association for Molecular Pathology in their submitted proposal to update CLIA:
https://www.amp.org/AMP/assets/File/advocacy/Amendments%20to%20CLIA%20modernization%20legislative%20text%2011_7_23%20FINAL.pdf?pass=70.

How should Congress consider issues relating to the practice of medicine and its relationship with labeling for LDTs? Should there be additional oversight of the information conveyed to patients serviced by LDTs?

LDTs represent the professional practice of laboratory medicine. LDTs are processes and procedures (not a manufactured device or kit) that are developed and performed under the oversight of board-certified, highly trained MD and/or PhD healthcare professionals as part of their health care practice. This is similar to other diagnostic processes in the laboratory (identifying a microbe, evaluating a microscopic slide, working up an autoimmune disease or blood product mismatch).

Requirements for information conveyed to patients is already addressed in Regulation 42 CFR 493.1291 which provides standards for information that must be included in the patient test report. Many of the current concerns with LDTs are related to provider-patient education (or lack of) re: the meaning of LDT results and are not about the actual performance of the test.

Should certain CLIA regulations be updated, would it necessitate a reevaluation of the CLIA fee schedule?

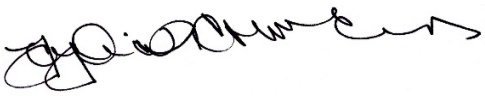
CLIA has not been updated in many years. Like any policy, procedure, or regulation, regular review and updating to meet changing times is important to high quality performance, and CLIA is no exception. To ensure an evidence-based review and full consideration of contemporary practice (including challenges), and emerging trends, the APC has recommended a national landscape project of laboratory practices that would include data-gathering, and development and testing of various regulatory scenarios, financial impact, and feasibility. This was included in our written response to the FDA regarding its proposed rule. Important areas to be addressed include molecular diagnostics, the role of biostatisticians, and computational approaches, including AI/ML. Changes to fee schedule should be considered within the context of this larger review.

What compliance challenges would legislative reforms to CLIA create? How should new regulatory requirements apply to tests currently available to patients?

New requirements should be folded into existing accreditation checklists and inspections by CLIA-approved entities such as CAP, NYS, and AABB. A period of education would be necessary to ensure laboratories have the knowledge and familiarity necessary to be compliant. Grandfathering certain aspects would also need to be considered; areas could be identified as part of a landscape project.

Thank you again for the opportunity to provide our views and perspectives on this important issue. The APC is happy to answer further questions or to serve as a resource as needed.

Sincerely,



Lydia Pleotis Howell MD
Deputy Director, Association of Pathology Chairs
Distinguished Professor emerita and Chair emerita
Department of Pathology and Laboratory Medicine
University of California Davis School of Medicine

Michael Laposata MD PhD
President, Association of Pathology Chairs
Professor and Chair
Department of Pathology
University of Texas Medical Branch
Galveston, TX

cc: Steven Kroft, MD, Advocacy Committee Chair, Association of Pathology Chairs
Karen Kaul, MD, PhD, Advocacy Committee Vice Chair, Association of Pathology Chairs