COLLEGE of AMERICAN PATHOLOGISTS

April 19, 2024

Honorable Shalanda D. Young
Director
Office of Management and Budget
1650 Pennsylvania Avenue, NW
Washington, DC 20500

Re: HHS/FDA Final Rule, “Medical Devices; Laboratory Developed Tests”

Dear Ms. Young,

The College of American Pathologists (CAP) appreciated the opportunity to discuss our concerns with the Office of Management Budget (OMB), Department of Health and Human Services, and Food and Drug Administration officials on April 18, 2024, regarding the proposed rule entitled, “*Medical Devices; Laboratory Developed Tests (LDTs)*.” We are providing this written summary of our concerns and ways that we believe oversight of laboratory-developed tests (LDTs) by the FDA could be improved. 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 has been constructively engaged for over a decade with the FDA, Congress, and multiple stakeholders on developing a framework for oversight of LDTs. Our position has always been to put patients and quality first – all LDTs should be safe and effective. We’ve also consistently felt that the FDA is the appropriate agency to oversee LDTs.

LDTs are developed and used in a single clinical laboratory to meet a specific clinical need. These tests are developed almost always because there is no FDA-approved or -cleared test that meets the specific clinical need in question. Most LDTs are developed and used for local patients being cared for in the hospital or health care network where the laboratory is located.

Although many LDTs represent innovations in patient care, most utilize well-established laboratory methods that medium- and large-sized laboratories already have much experience using. The CAP strongly believes that any LDT regulation must allow this innovation to continue and must not introduce overly burdensome or costly requirements for the laboratory. Stifling innovation and burdening laboratories would lead to many having to stop developing LDTs—depriving their patients of these lifesaving tests.

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This is why we, along with most of the clinical laboratory community, have significant concerns with the proposed rule released by the FDA in October 2023. We believe the proposal, as written, would significantly reduce the number of highly accurate LDTs available to patients and delay medical innovation and timely patient care. The proposal would not allow for sufficient flexibility in how the FDA oversees these tests.

Overall, we think the FDA should be focused mostly on tests that pose the highest risk to patients. We also believe that the highest risk LDTs represent a very small fraction of the total number of LDTs in need of significant oversight from the FDA. From our perspective, the right balance would have the FDA exercising full regulation of only the highest risk LDTs, with sufficient flexibility in its oversight of these and all lower-risk LDTs. The proposed rule, as written, would not allow the needed level of flexibility and would, thus, significantly restrict patient access to these vitally important tests. To that end, the CAP has worked with the FDA, Congress, and multiple stakeholders over several years to help develop a reasonable and balanced regulatory framework that would ensure quality testing for patients and minimize the regulatory burden on laboratories.

We are aware that some stakeholders are proposing that LDTs be regulated totally by the CMS, under CLIA guidelines, and that CLIA should be legislatively modified to allow this oversight by the CMS. As noted previously, the CAP continues to view the FDA as the appropriate agency to oversee LDTs. We also feel strongly that legislatively overhauling CLIA would risk severely disrupting the framework under which clinical laboratories have provided high-quality testing for decades.

CAP FDA LDT PROPOSED RULE CONCERNS

In our detailed comments to the FDA in December 2023, we listed multiple improvements we would like to see made in the proposed rule. The following are some of the key recommendations we included in our letter.

Grandfathering

Our first strong recommendation was for LDTs already being used prior to full implementation of the FDA rule to be “grandfathered” – in other words, allowed to continue to be used without having to submit these tests to full FDA regulation. The FDA has estimated that there are from 40,000 to 160,000 LDTs currently in use. We believe the actual number may be even higher. The burden on both the clinical laboratories and the FDA to subject these existing LDTs to full FDA oversight would be absolutely unacceptable.

Manual LDTs

Special immunohistochemical stains used to diagnose essentially all cancers in tissue specimens and currently performed in the majority of laboratories are regarded as non-manual LDTs by the FDA definition and, thus, would not be granted an exemption in the proposed rule. As new knowledge of cancer becomes available, new stains of this type must continue to be developed and used by

laboratories and the FDA proposed rule, as written, would make it very difficult for laboratories to continue to develop and use the latest stains in their cancer diagnoses.

Another prominent example is flow cytometry. Hematopathologists, for example, have safely and effectively used and interpreted flow cytometric analysis for decades in diagnosing leukemias and lymphomas. Flow cytometric analysis is another example of a test that the CAP feels should meet the definition of a manual LDT, particularly the interpretive part of this analysis, yet the proposed rule would classify this type of LDT as non-manual and therefore subject to full FDA regulation. We believe immunohistochemical stains, flow cytometry, and other similar tests that involve pathologist interpretation should be classified as manual LDTs and exempt from full FDA oversight.

LDTs Developed in Limited Numbers by Local Laboratories for Use by Local Patients.
In the proposed rule, questions were asked about whether academic medical center laboratories should be exempted from full FDA oversight of their LDTs. We believe that the same exemption as proposed for academic laboratories should be extended to **all** qualified laboratories when developing LDTs in limited numbers for use by local patients cared for in the community hospital or health care network where the laboratory is located. These laboratories have the same expert pathologists and the same technical know-how as academic laboratories. Not extending this type of exemption to these local laboratories would deprive their patients of ready access to LDTs. Many such laboratories are not located near an academic medical center, meaning that the patients they serve would be significantly disadvantaged.

Risk Classification
Another concern with the proposed rule is how many LDTs would be classified as being high-risk to patients. Based on the language contained in the proposed rule, and in the statutory guidelines under which the rule was developed, we're very concerned that many LDTs would be classified as high-risk that we believe, because of many mitigating measures available for these LDTs, should be classified at most as moderate-risk. We believe the highest-risk LDTs should only be those performed using non-standard, proprietary, and/or non-transparent methods and algorithms and for which there is no way to externally verify their accuracy, such as what happens with proficiency testing. Using the definition of high-risk as included in the proposed rule and the FDA's current statutory authority, we're very concerned that too many LDTs would be classified as high-risk and require full FDA oversight, including full pre-market approval.

Stakeholder Engagement and Public Meetings
In addition, we added a recommendation to our comments to the FDA in December that there should be more opportunities for stakeholder engagement before the rule is finalized and certainly before parts of the rule are implemented. An example of needed stakeholder engagement would be for the FDA to hold public meetings to discuss risk classification of categories of LDTs. We believe this discussion of risk classification would very much benefit from significant input from stakeholders, particularly those knowledgeable of the technical details of the LDTs in question and the existing medical literature pertinent to these LDTs.

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CAP MEMBER CONCERNS

The CAP has heard many concerns from our members on the impact this final rule with have on their practices and patients. If the proposed rule is unchanged and finalized, it will have a catastrophic impact on the clinical laboratory community. The high administrative burden and huge cost associated with complying will force many laboratories to stop testing and consequently negatively impact patient access to critical testing to the detriment of patient care. This will disproportionately affect rural and medically underserves areas and populations. For example, in hospitals with liver, kidney, and pancreas transplant programs, the impact on patient care could be profound. A rare complication of liver transplantation is acute graft versus host disease and the mortality is 50-80%. Donor chimerism, using short tandem DNA repeats, is an LDT used to help diagnose and treat GVHD. We are not aware of an FDA-approved or cleared test and even if a laboratory wanted to submit the test to the FDA for approval, its volume is so low (5 or so per year) that it would be too cost prohibitive. Sending the test to another laboratory would add unacceptable delays as we would immediately need to transfer the patient to a higher level of care and lose precious time.

Our pediatric pathologists are also extremely concerned, not only about rare genetic tests, but also about more common tests that are not FDA approved for pediatric patients but have been validated in their laboratories and thus become LDTs. The disruption in care to our youngest and most vulnerable patients is not acceptable.

From our experience as CMS-deemed accreditors, it takes at least one to two years for clinical laboratories to implement new regulatory and accreditation checklist requirements, given workforce challenges and reimbursement constraints. We repeatedly communicate and provide extensive educational resources to support implementation for even simple and straightforward changes. The implementation (depending on the regulation) may also be a phase one deficiency (less serious) for one or two years to give the laboratories time to adapt. Our members are extremely concerned about the plan for education and implementation once the rule is finalized. We hope the FDA will be cognizant of the challenges posed by this rule and will overeducate and provide necessary resources to the pathology and laboratory community.

The pathology community is concerned about the FDA resources proposed for use in helping clinical laboratories find and determine low-, moderate-, and high-risk test categories in the agency's framework. The premarket or post-market requirements associated with those risk classifications will require costly resources to comply with filing requirements. Many clinical laboratories cannot afford the resources and the staff needed. These laboratories will be forced to discontinue testing. We have asked the FDA to work with the laboratory community to ensure clinical testing is not disrupted and remains available particularly in rural or underserved communities.

SUMMATION

The CAP included multiple other concerns in our written comments regarding the proposed rule, but in the interest of space in this letter we won't include those here. The CAP has followed three

overarching principles in all our efforts to help develop an effective way for the FDA to oversee LDTs. We believe any regulatory framework for LDT oversight should:

1. Provide great quality and patient safety,
2. allow innovative LDTs to continue to be developed and available for patients, and
3. minimize the administrative burden and costs for laboratories, so they can continue to offer these vitally important tests.

In summary, we have grave concerns with the proposed rule released by the FDA in October. We believe the rule, as written, would significantly burden clinical laboratories, making it very difficult and unacceptably costly for these laboratories to continue to develop much-needed and innovative LDTs, resulting in patients being deprived of these life-saving tests. We believe a better approach would be to have a regulatory framework that would focus the FDA's resources mostly on the highest-risk LDTs and provide significant flexibility in their oversight of lower-risk LDTs to preserve quality, patient safety, innovation, and patient access.

We thank you for the opportunity to record the CAP's concerns with the proposed rule, as written, and to let you know how we believe oversight of LDTs by the FDA could be improved. If you need any additional information from us, please contact Helena Duncan, CAP Senior Director, Quality in our Washington office at hduncan@cap.org.

Sincerely,

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