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Michelle E. Tarver MD, PhD
Acting Director
US Food and Drug Administration
Centers for Devices and Radiological Health
Office of the Center Director
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Dear Acting Director Tarver:

The Association for Diagnostics and Laboratory Medicine (ADLM) is concerned that the May 6, 2024 final rule expanding Food and Drug Administration (FDA) oversight to laboratory developed tests (LDTs) will have a harmful impact on clinical laboratories and their ability to provide critical testing for their patients. While we wait for the courts and Congress to determine whether the agency has the statutory authority to regulate these tests, ADLM has compiled a list of questions that need to be addressed by the agency if these standards move forward:

What is an LDT

1. The FDA provided limited examples of "significant" modifications that would subject a test to premarket review and QS requirements. Does the FDA consider this list complete, and if not, when will additional guidance be released?
2. Will ANY modifications to an FDA-approved assay cause them to become an LDT?
3. Does the FDA believe that automating an FDA-cleared/approved test (for example, by placing it on a liquid handler) makes a test an LDT, even if the automation is replicating the manual steps as described in a package insert. Will the FDA be releasing additional guidance specific to the varying uses and applications of automation, and if so, when?

Pre-market Review

4. When an LDT is developed, can it be offered for clinical use while pending FDA approval, or must it wait for FDA approval before it can be used? Is the answer to this question different before and after the Stage 4 and 5 deadlines?
5. How long does the FDA envision it will take to approve a submitted LDT? Is the expected timeline different between 510k and PMA LDT submissions?
6. Does the FDA have a department for vetting/approving LDT submissions, and if not will a new department or division be established?

7. Typical FDA 510k protocols allow for ~10% of the samples to be "contrived" to reflect pathology. How will a 510k, de novo, or PMA for a rare disorder, affecting a few dozen patients worldwide, be evaluated when a majority of specimens must be contrived?
8. Does the FDA have internal expertise to evaluate the broad array of LDTs (e.g., mass spectrometry, genomics, flow cytometry) performed today?

Test Validation

9. Will the FDA be releasing additional guidance related to anatomic pathology and unique aspects of test validation and modification currently used to support tissue staining and diagnoses (e.g., optimization of antibody concentrations, fixation times, epitope retrieval, incubation times, and use of automation), and if so, when?
10. For LDTs that were in the middle of validation during the issuance of the final rule, all development work will have occurred prior to the Stage 3 requirement for 21 CFR 820 design history documentation. What guidance will the Agency provide for labs about retrospectively fulfilling these criteria (which appear to be designed in a prospective way)?
11. Many clinical labs have substantial capital resources invested in existing instruments that may be designated RUO, and replacement of these instruments would be an unsustainable financial burden. To date, rigorous quality and patient safety has been maintained through appropriate assay design, validation, ongoing quality control procedures, and proficiency testing. Will demonstration of overall system performance through the quality of the end results suffice for FDA, or will the Agency require a lab to obtain design history-level information for each of the instruments themselves if any new tests are developed using this instrumentation?
12. Outside of a PMA, is there a mechanism for evaluating the "clinical validity" of a test?

Third Party Review, Laboratory Compliance & Enforcement

13. How will the FDA assure that third party reviewers possess the necessary expertise to evaluate a broad array of LDTs, when device classifications for many of these tests have not yet been established by the FDA? Can a clinical laboratory use a third-party review if there is not an FDA device classification?
14. Does the FDA have a process for auditing premarket LDT compliance? Post market compliance? Will this be done by inspection? If not, how will FDA verify compliance?
15. The complaint file guidance is predicated on the definition of "distribution." Given that a lab procedure is being defined by the FDA as "manufacturing," what is the definition of "distribution," and how does that relate to the performance of the lab testing itself? Is "distribution" the distribution of a result, or is there an earlier line (e.g., making a buffer and putting it on an instrument is "distribution," running the (LDT) test is post-"distribution")?

16. Historically, failures of QC or PT have been treated as operational failures and addressed under CLIA. If they are post- "distribution" (see question above), do they need to be handled as a complaint (the lab complaining to itself as the manufacturer)?
17. Will the FDA be releasing clearing guidance on which issues clinical laboratory performing LDTs should be reporting as 'user facilities' and which issues clinical laboratories should be reporting as 'manufacturers'?
18. For purposes of manufacturer MDR reporting for an LDT, does the term "employees" refer to employees of an individual lab (the presumed manufacturer), employees of an enclosing Department of Pathology, or employees of the entire enclosing health system (with presumed documentation of training)?
19. In the final rule, the FDA notes that "*FDA intends to develop appropriately targeted enforcement discretion policies for certain common changes to IVDs (including those manufactured and offered by public health laboratories), such as extension of specimen stability and certain alternative specimen types, following good guidance practices*." As this information is essential for clinical laboratory planning efforts related to stage 1 (MDR) and stage 2 (listing), when will the FDA release these additional enforcement discretion policies?

General Questions

20. What is the process by which clinical laboratories are expected to submit labeling prior to the Stage 2 (May 6, 2026) deadline? Is there a process, form, or other method of submission that must be used?
21. What is the process for defining an "unmet" need? Can a need be partially met? Can an LDT fill the unmet portion without a requirement for filing?
22. Will the fees be per assay or per lab or per healthcare system?
23. Will the FDA be answering all questions submitted to the LDTFinalRule@fda.hhs.gov email address, and if so, when?

ADLM looks forward to working with you on this issue. If you have any questions, please email Vince Stine, PhD, ADLM's Senior Director of Government and Global Affairs, at vstine@myadlm.org.

Sincerely,

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President, ADLM