ASCLS
The American Society for Clinical Laboratory Science

Laboratory Developed Tests Should Be Carefully Regulated

Position:
We as clinical laboratory professionals agree that laboratory developed tests (LDTs) must be regulated to ensure their accuracy and overall patient safety. Patients and health care providers need accurate, reliable, and clinically valid tests to make good health care decisions. Inaccurate or false test results, or accurate measurements with an invalid claim regarding the test results' relationship to a disease, can lead to substantial patient harm. LDTs play an increasingly important role in the provision of high-quality health care, and many laboratories perform proper validation of their LDTs and provide high-quality, professional management of their operations. However, currently, patients and providers cannot uniformly rely on all tests offered for clinical use as some are not subject to active premarket oversight to ensure they provide accurate measurements and valid claims. Furthermore, the Centers for Medicare and Medicaid Services' (CMS) evaluation of clinical utility, as part of a coverage determination, would typically follow from Food and Drug Administration (FDA) review of analytical and clinical validity.

Background:
LDTs are defined by the FDA as in vitro diagnostic tests that are designed, manufactured, and used within a single laboratory. In 2014, the FDA released draft guidance to provide enhanced oversight of LDTs. FDA proposed a three-tier risk-based framework for this oversight. High-risk (Class III medical devices) and moderate-risk (Class II) LDTs would be subject to premarket review requirements (i.e., premarket notification, or 510(k) submissions), FDA registration, listing, and reporting requirements. Low-risk LDTs (Class I) and LDTs for rare diseases or unmet medical needs would be under FDA enforcement discretion for applicable premarket review and quality systems requirements; they would be required to comply with registration and adverse event reporting within six months of the release of FDA's final guidance.

On January 13, 2017, the FDA released a discussion paper on LDTs and announced that it would not issue a final guidance on the oversight of LDTs at the request of various stakeholders to allow for further public discussion on an appropriate oversight approach, and to give congressional authorizing committees the opportunity to develop a legislative solution.

Comments on the New Discussion Paper:

- The clinical laboratory personnel community appreciates the elucidation of the distinction between clinical validity and clinical utility. We define clinical validity as how well the test determines the presence, absence or potential risk of disease (i.e. the test's ability to detect the clinical condition for which the test in intended). We agree with FDA's assessment that clinical validity is very different from the clinical utility that CMS uses to determine coverage decisions and that CMS needs the information about clinical validity from FDA to protect the public.
- We agree that molecular tests are essential tools in diagnosis, prognosis, and therapy decisions, putting them in the category of high-risk tests. These LDTs require oversight. However, one might question whether the full burden of data required by the PMA process is even achievable. A balance needs to be struck between full regulation and providing potentially useful information to providers and patients with rare diseases.
- We agree that a risk-based approach to oversight is necessary and appropriate. We believe that a risk-stratified approach to regulation is also appropriate. Very low-risk traditional LDTs should not require full PMA/510k documentation.

- We support a phased-in process proposed. However, we do disagree with the Year One exemption of traditional LDTs from reporting of serious adverse events. While we feel that traditional LDTs are low-risk and unlikely to create serious adverse events, if such an event were to occur, it should be reported. Laboratories are familiar with the adverse event reporting process as it applies to FDA-approved tests and equipment, and reporting of all adverse events should not be a burden for either laboratories or the FDA.
- On the subsequent years of the phase-in, our previously stated concern about whether the full burden and quantity of data required by the PMA process are necessary or achievable. A modification of the PMA should be considered.
- There are several statements in the document that laboratories that conduct proper validation should not need to collect more data or incur new costs for LDT regulation. We feel this statement is too optimistic; the rigor and volume of data required by the PMA process are greater than the typical validation acceptable by CMS of an in-house test.
- We urge the FDA to address the issue of health system laboratories that may use the same methods and equipment. If an LDT is validated in one laboratory within a health system, we urge that the other system laboratories be allowed to adopt the method without repeating the full validation.
- We are concerned about what groups or agencies will be identified by FDA with which to expand its third party premarket review program. We do not believe that many of the CLIA accredited organizations have the expertise or experience needed to perform premarket reviews. Allowing and encouraging clinical collaboratives will be an excellent way to expedite data collection and sharing; all of which will enhance innovation rather than stifle it.
- We question whether it is realistic that a laboratory would be able to anticipate future changes needed to a test that is brand-new and has not been performed in a clinical setting yet. Some latitude should be incorporated into any oversight to avoid the need to re-submit a test following minor changes.
- We support the use of CLIA's quality system requirements for LDTs. We reiterate our stance that, if third party entities can inspect for the FDA requirements that are in addition to CLIA, that extensive education of State Department of Health and inspectors is necessary.
- We share the FDA's goal to balance patient protection with continued access and innovation.

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