FDA Announces Plans to Regulate LDTs

Agency aims to phase in a risk-based framework over 9 years

After notifying Congress in July of its intent to actively regulate laboratory-developed tests (LDT), the FDA is now seeking feedback on draft guidance, published on September 30, on a proposed framework to do so.

The FDA defines diagnostic tests—whether made by conventional device manufacturers or in laboratories—as medical devices, which can be regulated. To date, although diagnostics manufacturers have been subject to FDA surveillance, the agency has exercised "enforcement discretion," choosing not to similarly regulate LDTs. However, with the rapid evolution of the technology and marketing of LDTs, the agency has begun to worry about "the absence of appropriate oversight."

"The FDA is officially recognizing that a test is a test, with the same risk to patients no matter where it's developed," says Andrew Fish, executive director of AdvaMedDx, which represents the diagnostics industry.

"We don't have this inconsistent regulatory landscape with drugs, and I don't think we should for tests that direct therapy," says Daniel Hayes, MD, director of the breast oncology program at the University of Michigan.

Seeking to reduce the risk of harm to patients and avoid regulatory inconsistencies, organizations like the American Society of Clinical Oncology and the American Association for Cancer Research (AACR), which issued a policy statement in September, also favor greater FDA oversight (Clin Cancer Res 2014;20:4978).

However, the American Clinical Laboratory Association (ACLA), the leading advocate for clinical laboratories, staunchly opposes the FDA's move. "LDTs are the practice of medicine, not medical devices," so they shouldn't fall under the FDA's jurisdiction, argues Alan Mertz, ACLA's president. In addition, "taking cancer as an example, enormous strides are being made not just with targeted therapies, but with tests that pinpoint tumors at the molecular level. It would be tragic if overregulation stifles this innovation engine."

To minimize any negative impact on innovation, the FDA will phase in oversight of LDTs over 9 years. The agency plans to collect information on all LDTs through a formal notification process, then classify each as low-, moderate-, or high-risk. It will target the high-risk category first, including companion diagnostics and LDTs offered in lieu of FDA-cleared or -approved tests. Because these LDTs guide treatment decisions, their safety and clinical utility should be validated, the guidance document states; however, physicians may continue ordering these tests while they are reviewed.

Oversight of moderate-risk LDTs will begin 4 years after the guidance is finalized; enforcement discretion will still apply to low-risk LDTs and those for unmet medical needs. Also, the FDA will not preclude academic labs from developing LDTs for investigational purposes.

Mertz doesn't think the FDA is equipped to efficiently examine existing LDTs—there are "tens of thousands," he estimates, from as many as 11,000 labs. Unless additional fees are imposed, explains Scott McGoohan, ACLA's director of reimbursement and scientific affairs, it's unlikely that the agency can review more than a dozen annually.

Meanwhile, Hayes believes raising the approval bar for LDTs "should go hand in glove with reimbursement."

"If test approval becomes more time-consuming and stringent, without proper reimbursement," he says, "then it's capitalism 101; people will walk away and the LDT field will see no progress. But with the FDA's proposal, I do believe there'll be less smoke and more fire [properly validated LDTs]."

EMPHASIZING CLINICAL VALIDITY

Whether a test possesses clinical validity—meaning it's demonstrably linked to a specific disease or biological function—is central to the FDA's decision to begin regulating LDTs. To date, the Centers for Medicare and Medicaid Services (CMS) has been responsible for LDT oversight through the Clinical Laboratory Improvement Amendments (CLIA) program. CLIA does not require or assess any LDT's clinical validity, and adverse event reporting—which the FDA will also enforce—is not mandatory. Rather, CLIA focuses on high-quality lab practices and sees that tests measure up to performance characteristics, including precision and reproducibility.

Such analytical validity is important, but insufficient, from the FDA's perspective. The agency believes CLIA oversight "alone does not ensure that LDTs are properly designed, consistently manufactured, and are safe and effective for patients."

McGoohan points out that most labs performing LDTs are subject to oversight by multiple groups, not just CLIA. For example, he says many are also accredited by the College of American Pathologists, which requires documentation on clinical validity. Rather than involve the FDA, he favors an expansion of CMS's authority, believing CLIA is a better fit for oversight for clinical labs.

Others view the FDA's role as "different in focus, scope, and intended to be complementary," Fish says. "It's appropriate for them to regulate LDTs, especially in terms of clinical validity, because unlike CMS, they have the necessary expertise."

Hayes agrees. "To me, an LDT lacking high-level evidence of improved clinical outcomes is as bad as a bad drug," he says. "Just because a test is used doesn't mean it should be."

Similarly, Charles Sawyers, MD, the AACR's immediate past president, cautions that for cancer patients, the consequences of incorrect recommendations based on faulty LDTs—losing the opportunity to receive a potentially more effective therapy, for example—are unacceptable.

"Having a single, strict regulatory approval standard," he said during a recent congressional committee hearing, "will reassure the American public that [LDTs], regardless of origin, are safe, accurate, and effective." *–Alissa Poh* ■

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