MEDTECH INSIGHT
CITELINE COMMERCIAL

01 Dec 2023 | **News**

FDA Receives Thousands Of Opinions On Proposal To Regulate LDTs As Comment Period Comes To A Close

by Brian Bossetta

As the US FDA works to finalize new regulation of lab-developed tests, it must consider more than two thousand comments that have poured into the agency since the proposed rule was published in October. The comment period closes Monday.

The US Food and Drug Administration's proposal to regulate laboratory-developed tests (LDTs) will either ensure patients receive accurate results they can depend on for making critical health decisions, or it will cripple diagnostics leading to significant patient harm.

These divergent predictions represent the contrast of views that have flowed into the agency since it published its proposed rule on regulating LDTs in October. To date, the agency has received 2,107 comments from a variety of stakeholders, both for and against; and despite requests to extend the comment period — a request the FDA often grants — the 4 December deadline remains.

In exercising its rulemaking authority, the FDA is proposing to phase out its general discretion of LDTs over four years, which will place them under the same regulatory purview as other in vitro diagnostics (IVDs). (Also see "*Proposed Rule Would Apply FDA's Diagnostic Rules To LDTs*" - Medtech Insight, 29 Sep, 2023.)

The FDA's contention all along has been that it needs to regulate LDTs due to several factors, such as the growing complexity of the tests and the agency's obligation to provide the public with some level of assurance they are safe, effective, and reliable.

Another reason the agency has often cited is that LDTs are not centrally registered or tracked, which makes it difficult to know how many of them are currently on the market and how they

perform in comparison to FDA-reviewed diagnostics.

> *"Too often there is an assumption that because a test is available for clinical use, the test has been demonstrated to generate accurate and reliable results." — Elizabeth Mansfield*

Moreover, inaccurate results from more sophisticated and higher-risk LDTs, the FDA has argued, could lead patients to pursue unnecessary treatments or fail to get needed ones. LDTs today are marketed to diagnose conditions as complex as heart disease, various cancers, autism, and Alzheimer's.

Not Buying It

But these arguments are weak and not in line with the practical realities of developing LDTs, according to Romney Humphries, division director of laboratory medicine at Vanderbilt University Medical Center, who spoke to *Medtech Insight* about the proposed rule and its likely impact on labs, industry, and patients.

Humphries said her opposition to the FDA's proposed rule is based mostly on how she sees it affecting her specialty, infectious diseases. She believes it will have a profoundly negative impact on the ability of providers to care for patients.

> *"We are concerned that if the proposed rule proceeds, it will hinder clinical decision making for patients struggling with cancer, infectious diseases, rare diseases, and genetic disorders and may lead to worse health outcomes." — David Louis*

As she explained, there are few FDA-cleared diagnostics for infectious diseases, mainly because of a lack of demand that limits the incentive for industry to develop them — due also in large part to the complexity of the infectious diseases they are designed to detect.

"There are literally thousands and thousands of bacteria, fungi, parasites, and viruses that can

cause infections and they are constantly evolving and we're constantly seeing new ones come about, such as COVID-19, which I think everyone is familiar with," Humphries said. "Much of what we do in infectious diseases labs is take FDA-cleared tests and adapt them for a more expanded sample type, such as a respiratory diagnostic for other parts of the body."

In her view, FDA oversight will hamper this process.

But Humphries also disagrees with the FDA's argument that a uniform regulatory standard is needed to track LDTs to ensure they are on par with other diagnostics the agency reviews.

"There's already a lot of due diligence those goes into implementing these tests," she said, noting LDTs are currently regulated by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA), federal standards regulating testing facilities enacted in 1988. "Part of CLIA requires that when you develop a new test, or even when you are implementing one that is FDA-cleared, you have to do a lot of work in your lab to confirm that it's going to work for your targeted patient population."

Rulemaking Can Only Do So Much: Stakeholders Weigh In On LDT Rule

By Hannah Daniel

11 Oct 2023
Investors and business executives weighed in on the FDA's proposed rule on LDTs during a panel at the Medtech Conference on 9 October.

Read the full article here

Humphries pointed out her lab is accredited by the College of American Pathologists, which requires all labs to register their LDTs. They are then reviewed during inspections — a rigorous process, she added.

"Inspectors scrutinize these LDTs thoroughly. And we have a lot of controls and quality systems in place to make sure that we're monitoring and tracking performance," she said.

For example, in a review she conducted at Vanderbilt, Humphries said there were more issues with FDA-cleared tests than LDTs.

"That's not to say lab-developed tests never have problems, just like it's not to say that FDA-cleared tests never have problems," she said. "But I think it makes the point that just because something is cleared through the FDA does not guarantee that there are no problems with that test down the road."

Validation Needed

On the other hand, Elizabeth Mansfield, vice president of regulatory policy at Foundation Medicine, commended the agency for addressing the safety risks posed by "poorly validated LDTs."

The quality and level of validation of tests used to select therapy can vary dramatically, Mansfield said in her comments, adding that Foundation Medicine has observed poorly validated testing that incorrectly identified patients as positive or negative for biomarkers. In these situations, she noted, patients may have lost the opportunity to try a potentially life-saving therapy or been exposed to a potentially toxic therapy with no benefit.

"Too often there is an assumption that because a test is available for clinical use, the test has been demonstrated to generate accurate and reliable results," Mansfield said. "Such assumptions are flawed and will perpetuate, if not exacerbate, the known quality gaps in tests used in clinical practice today."

> *"The FDA regulation of LDTs will ensure that doctors, patients, and consumers are getting results that are reliable and clinically meaningful." — Marian Manapsal*

She added that Foundation Medicine has experienced situations where its testing identified an incorrect diagnosis. She described one such incident in which a patient was initially misdiagnosed with lung cancer, but through additional Foundation Medicine testing was found to have biomarkers consistent with metastatic skin cancer treatable with an FDA-approved targeted therapy.

"As a company committed to offering the highest-quality genomic testing, Foundation Medicine supports a single, risk-based regulatory framework for all tests, regardless of where the test is manufactured," she said. "Foundation Medicine supports a modernized regulatory framework that enables future scientific research to drive medical discoveries, translates those discoveries to the clinical setting, and improves patients' access to personalized care."

Finding the Balance

But David Louis, pathologist-in-chief, Massachusetts General Hospital and pathology professor at Harvard Medical School, voiced his disagreement with the FDA applying the existing medical device regulatory framework to LDTs, especially to CLIA-certified LDTs that are developed and used within a single laboratory for a hospital or health system.

"We are concerned that if the proposed rule proceeds, it will hinder clinical decision-making for patients struggling with cancer, infectious diseases, rare diseases, and genetic disorders and may lead to worse health outcomes," Louis commented.

Yet, Louis also said he understood the FDA's need to oversee LDTs "as well as strike the right balance in ensuring patient safety while optimizing patient care and fostering responsible innovation."

To that end, he said the FDA should develop a new regulatory paradigm for LDTs that more appropriately captures the complex and unique nature of LDTs. Specifically, he urged the FDA to adopt a risk-based framework that incorporates distribution patterns. Using medical device framework as proposed is insufficient, according to Louis, because it fails to address the risk associated with the level of distribution of the test.

"For example, tests that are widely distributed for commercial purposes direct to consumers have a different level of risk than tests that are not distributed outside a hospital and used only under the guidance of a clinician," he wrote, adding the FDA is familiar with making such distinctions when it comes to pharmaceuticals, such as over-the-counter drugs versus prescription ones. Louis believes the FDA should do the same with LDTs.

> ***"Patient populations are different, which means the care they need is different. And what enables us to care for patients at a local level is our ability to custom tailor our testing to meet their needs."***
> ***— Romney Humphries***

Louis further recommended the FDA seek "greater clarity" for risks associated with rare diseases, infectious diseases, public health emergencies, and existing tests with no adverse event profiles. He would also like to see the FDA extend the proposed phase-in period, doubling it from four years to eight.

Louis also proposed the FDA establish "national accuracy laboratories" to serve as independent entities for evaluating and verifying the performance of diagnostic tests as well as guidance.

And lastly, "to reduce regulatory burden and facilitate timely reviews," the FDA should develop practical frameworks, such as specific reporting tables tailored to distinct technologies and testing modalities.

“These frameworks can simplify the preparation of regulatory submissions and updates, while also capturing the essential performance characteristics of LDTs,” Louis said. “By developing and providing standardized templates, FDA can expedite the review process and ensure that all necessary data is presented in a consistent and readily understandable format.”

Data

Joseph Eron, Christopher Hurt, and David van Duin, professors of medicine in the division of infectious disease at the University of North Carolina at Chapel Hill, said that rulemaking in the absence of comprehensive data on the use of LDTs and their impacts on patient care will severely restrict patient access to essential, high-quality LDTs, thereby leading to missed or delayed diagnoses and worse patient outcomes.

The professors urge the FDA to delay requirements in the proposed rule regarding LDT requirements associated with 510(k) premarket notification or premarket approval (PMA), quality system (QS) regulation, and labeling until more complete data on LDTs are compiled and made publicly available.

The rule also proposes high-risk LDTs submit a PMA no sooner than 1 October 2027, with low- and moderate-risk tests required to submit a 510(k) on or after 1 April 2028.

“While there are concerning examples of faulty LDTs that should be addressed, FDA has not yet collected comprehensive information about what LDTs are in use and how they are impacting patient care,” the professors said. “It would be inappropriate to base sweeping regulations on individual examples rather than first collecting a comprehensive data set that reflects the wide range of uses of LDTs.”

Further, they recommended FDA only move forward on its proposal to phase out enforcement discretion for registration and listing requirements and medical device reporting for LDTs.

This approach, the professors argue, will provide the necessary data regarding the full scope of LDTs currently in use and their positive and negative impacts on patient care while allowing the FDA to better determine an appropriate regulatory framework based on risk.

Too Aggressive

The proposed four-year phase-in, which Humphries described as “extremely aggressive,” is one of the aspects of the rule that concerns her the most along with a lack of concessions such as grandfathering for existing tests, carve outs for rare diseases, or a risk-based approach to evaluate LDTs.

“All of these are really important to make sure that we don't have serious unintended consequences,” Humphries said.

Another question raised by several voices has been whether the FDA has the authority to unilaterally place LDTs under its purview. Despite repeated claims by the agency, including directly from Commissioner Robert Califf, that it would have preferred a legislative solution to the LDT question, it appears the rule will be finalized unless Congress steps in, which is certainly possible.

The VALID (Verifying Accurate, Leading-edge IVCT Development) Act, which Congress failed to pass last year, and which would have settled the LDT question, was reintroduced in the House in March. The sponsors, representatives Larry Bucshon, R-IN, and Diana DeGette, D-CO, said the legislation provides "a safe, accurate, and risk-based framework" for LDTs while allowing room for innovation. (Also see "*Rulemaking Can Only Do So Much: Stakeholders Weigh In On LDT Rule*" - Medtech Insight, 11 Oct, 2023.)

Some have suggested the FDA's flexing its regulatory muscle — whether intentional or not — is a shot over Congress' bow which may motivate it to finally act on diagnostic reform and put the issue to rest.

"Yes, I've heard that too," Humphries said, adding her skepticism that the FDA had the bandwidth to take on the additional task of regulating LDTs.

Elizabeth Hillebrenner, associate director for scientific and regulatory programs at the FDA's Center for Devices and Radiological Health, addressed this issue during a webinar last month. Hillebrenner said the agency was working to enhance its third-party review program, which was reauthorized under the latest Medical Device User Fee Amendments, or MDUFA V, and could be used extensively for LDTs.

But critics doubt that's sufficient, citing the FDA's inability to cope with its workload during the pandemic. Even with third-party review the influx of LDT submissions would amount to too much being added to the FDA's already full plate, they say. (Also see "*Hillebrenner Fields Questions On FDA's Proposed Rule To Regulate LDTs, Says No To Extended Comment Period*" - Medtech Insight, 2 Nov, 2023.)

Patients

But regardless of the legalities or the politics surrounding whatever the final rule is or isn't, Humphries questions the wisdom of the FDA taking on the role of LDT regulator.

"I don't necessarily agree that it's the role of the FDA to regulate lab-developed tests," she said, adding that when all is said and done it might not only harm patients, but the most vulnerable ones.

Speaking again through the lens of her specialty, Humphries emphasized infectious diseases are

often regional with infections in Tennessee, for instance, different than those in California.

“Patient populations are different, which means the care they need is different. And what enables us to care for patients at a local level is our ability to custom tailor our testing to meet their needs,” she said. “But when you're working through a system that’s national for something that has a good return on investment, you lose the ability to do a lot of customization.”

And several microbiologists agree with Humphries’ point on the proposed rule’s inadequacy to address the uniqueness of infectious diseases.

Sheri Hohmann, an assistant professor of microbiology at the University of Utah, Shangxin Yang, a clinical microbiologist at UCLA Health, Lucas Osborn, a microbiologist at Children's Hospital Los Angeles, and Brandon Ellis, a microbiologist at Johns Hopkins Hospital, submitted nearly uniform comments expressing concern that instead of ensuring the safety and accuracy of LDTs, the proposed rule might have the opposite effect “by limiting patient access to vital testing for pathogens.”

> *“It's not good when you can go to two different cancer centers and get two different answers when your life depends on it.” — Robert Califf*

But with the comment period on the eve of closing, the FDA is holding firm to its commitment to regulate LDTs which it believes is in the best interest of public health.

During a fireside chat hosted by the Alliance for a Stronger FDA earlier this year, Califf said Americans needed a framework of quality and laboratory testing that assures reliability.

“You ought to be able to get a reliable test, where the operating characteristics of the test are understood because none of these tests are perfect,” he said. “It's not good when you can go to two different cancer centers and get two different answers when your life depends on it.”

But with all the voices, both pro and con, speaking out on the proposed rule, perhaps none are more important than those of patients.

Marian Manapsal voiced her support for the proposed rule because she wants to know the tests she relies on for her health decisions are accurate.

“The FDA regulation of LDTs will ensure that doctors, patients, and consumers are getting results that are reliable and clinically meaningful,” Manapsal said. “This proposed rule is designed to ensure that critical clinical decisions rest on secure evidence."

Kathryn Dean, however, pleaded with the FDA to leave well enough alone, describing in detail her 6-year-old daughter’s life-threatening illness that went undiagnosed despite the best treatments available.

Dean said her daughter was examined by doctors at six different children’s hospitals across the country, received a battery of tests, was in contact with several specialists around the world, and was accepted into the National Institutes of Health undiagnosed diseases program — yet her daughter’s mysterious illness remained unsolved.

Finally, an LDT at Nationwide Children’s Hospital revealed a genetic alteration that was making her daughter sick. That test, Dean wrote, enabled her daughter’s doctors to tailor her immune system to fight her specific disease and enabled her daughter’s team to treat others with the same disease.

“If access to these tests is not available, there will be countless families that will not get the treatment for their children that I received,” she said. “Please do not take this gift of finding an answer and treatment plan away from sick children or their families.”