Coronavirus Testing Delays Yield New Oversight Bill, Shine Light on LDT Regulation Debate

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Rep. Diana DeGette, a sponsor of the VALID Act

NEW YORK – Earlier this month, lawmakers introduced a bill that would vastly change the oversight system for diagnostics in this country and give the US Food and Drug Administration explicit authority to regulate tests developed by labs.

The bipartisan sponsors of the Verifying Accurate, Leading-edge IVCT Development (VALID) Act have claimed that their legislation will streamline regulations and speed access to tests in public health emergencies like the present COVID-19 pandemic.

However, it is an odd time to advance a bill that would place the FDA at the helm of an entirely new oversight framework for diagnostics, since some public health and lab industry experts are blaming the agency for over-regulating labs and hampering early efforts to track how the SARS-CoV-2 virus spread throughout communities.

Most industry observers are still considering VALID, but many remain concerned that in the hands of the FDA, the lab industry would be overburdened with regulation and no longer nimble in the face of advancing science or a sudden public health crisis. On the other hand, there are those like lab industry veteran Robert Boorstein, who pointed out that the supply chain issues hampering test roll out currently actually suggests the need for a centralized authority and more standardization. He is of the view that even if the FDA had allowed lab tests to enter the market earlier, it would not have helped with the present reagent shortages that labs around the country are facing.

The FDA and clinical labs have a contentious history. The FDA has always maintained it has authority to regulate all diagnostics, including lab-developed tests (LDTs). Meanwhile, the lab industry has argued that while the law allows the agency to regulate medical devices, the tests performed by labs are not devices but more akin to "the practice of medicine" outside of the agency's authority.

To further complicate matters, the FDA, while maintaining it has authority over LDTs, has exercised "enforcement discretion" over them, leaving oversight responsibilities to the Centers for Medicaid &

Medicare Services. CMS is responsible for ensuring labs meet federal laboratory standards outlined in the Clinical Laboratory Improvement Amendments (CLIA). That means that as long as LDTs are performed in CLIA-certified labs, labs can market them without first seeking premarket approval or clearance from the FDA. This has largely suited labs, since they believe that the FDA's device regulations do not address the work that they do and that the agency's policies would make it difficult to keep LDTs up to date with the latest science or emergent public health needs.

However, from time to time, when the agency felt that an LDT or a subset of LDTs puts the public health at risk, it required labs to either submit their tests for premarket review or to stop selling them. This piecemeal regulation has created an uncertain regulatory environment for labs for around three decades, say policy experts, and is at least part of the reason for the FDA's fumbles during the current pandemic.

"One of the problems of not having clarity upfront about whether an agency has authority to or will in fact regulate an industry is that it creates confusion, both within the government and by regulated entities, about who is or should be taking the lead, which prevents both industry and regulators from being nimble" said Gail Javitt, a director at Hyman, Phelps & McNamara specializing in FDA regulation for diagnostics, devices, and drugs. "Everyone is trying to figure out how to proceed while the clock is ticking."

Given the FDA's history of shutting down lab testing, when it became clear in January that SARS-CoV-2 virus had reached the US, lab professionals said they were hesitant to launch LDTs. They were unsure if the agency would practice "enforcement discretion." A few weeks later, the FDA made its position clear. After a faulty reagent hampered the rollout of the first test kits from the US Centers for Disease Control and Prevention to public health labs around the country, the Association of Public Health Laboratories requested the FDA to practice "enforcement discretion" and allow its members to develop LDTs to meet testing needs. The agency declined, and subsequently highlighted the public health risk if results from tests deployed in an emergency are wrong.

In explaining how it regulates, the FDA often speaks of making a risk/benefit calculus. This involves weighing the public health gains from providing access to a healthcare product against the risks or potential harms if that product should malfunction. Its critics say the FDA failed to strike the right balance in the present public health crisis. The FDA, meanwhile, has repeatedly defended that it has been flexible with regulations and has worked closely with labs and commercial manufacturers to expedite test access and approve EUAs the same day or even faster.

In the past, the FDA has rationalized that it was restricting access to certain LDTs in order to prevent public harm, Javitt said, but "this episode shows, there can also be significant harm to public health from preventing access."

At a clinical lab industry meeting earlier this month, FDA Commissioner Stephen Hahn said that there are lessons in the present public health crisis about how the agency should balance patient access and safety in regulating tests going forward. The next day, Reps. Diana DeGette (D-Colorado) and Larry Bucshon (R-Indiana) introduced the VALID Act.

When the bill was released on March 5, Bucshon argued that during a public health crisis the government must act quickly to ensure hospitals and labs can develop tests to identify those infected and stop the spread of the virus. He added that VALID "will overhaul the federal government's outdated system that is slowing down our ability to respond to these threats."

The framework described in the bill features new mechanisms such as technology precertifications and broad grandfathering and exemption criteria aimed at streamlining the regulatory process and making regulations less burdensome for labs. Importantly, the legislation, which was heavily influenced by the FDA, would end uncertainty around "enforcement discretion" by categorizing all diagnostics, including LDTs, as in vitro clinical tests (IVCTs) and bringing them under the agency's oversight.

Experts in the lab and pathology community, preoccupied with responding to the public health crisis, have not had much time to respond to the bill. Given how much criticism has been volleyed at the FDA for its handling of the coronavirus testing rollout, a bill that would give the agency explicit authority to oversee all tests in emergencies and non-emergencies may not have an easy path through Congress, particularly in an election year.

"There is a risk that this bill could be politicized. Right now, the clinical labs themselves are focused on developing and distributing coronavirus tests, and making sure tests are done correctly and the results are quickly reported," warned Amy Miller, a diagnostic policy expert and CEO for the Society for Women's Health Research.

"We're seeing the different parts of the lab industry in the public eye now. The CDC and public health labs are different from [large reference labs like] Quest and LabCorp, which are different from other academic and community labs. They operate differently and have different capacity," she said. "The [impact] of this bill on the broader industry truly needs to be thought through."

Not like other pandemics

It is the Food, Drug, & Cosmetic Act which gives the FDA its power to authorize the use of both unapproved tests and tests previously approved for other uses for the assessment of pathogens in an emergent public health crisis. Test providers must apply for Emergency Use Authorization (EUA) and submit evidence demonstrating the accuracy of diagnostics under an expedited process.

Since the CDC usually has the first access to samples from infected patients, it is typically able to develop the first test under EUA. This test is deployed at public health labs around the country, and then other commercial tests come on the market. For example, during the novel influenza A (H1N1) virus outbreak in 2009, the CDC identified the first infected patient on April 15 and three more infected patients over the next week. The CDC uploaded the viral sequence to public databases on April 24. The government declared a public health emergency on April 26, and the CDC received EUA for its test the next day. By May 1, CDC's test kits were deployed to public health labs, and in subsequent months other commercial test kits received EUA.

This basic system seemed to serve the country well until SARS-COV-2. By all accounts, regulators, immunologists, and lab professionals on the ground agree that COVID-19 is not like prior outbreaks.

"This emergency is different and requires a different response," Hahn acknowledged at the American Clinical Laboratory Association's annual meeting earlier this month. SARS-CoV-2 is spreading through the world much faster than other recent pandemics. Since Chinese authorities reported the first cluster of pneumonia cases in Wuhan, Hubei Province, on Dec. 31, Johns Hopkins University's Coronavirus Resource Center estimates there have been around 169,400 confirmed COVID-19 cases and more than 6,500 deaths around the world.

"It's hitting pretty intensely, and the global spread is impressive," said Boorstein, medical director for oncology and esoteric testing at Brooklyn, New York-based Lenco Diagnostic Laboratories. "In terms of people's life-altering events, this is already up there. You have the features of the 2009 financial crisis and all the anxiety of AIDS, compressed into about a month."

Depending on the age demographics of the region, the mortality rate ranges from 0.7 percent in South Korea to as high as 7 percent in some parts of Italy. At the time this article was published, more than 3,600 people in the US had tested positive for the virus, and 69 people had died. But because only an estimated 41,000 tests have been performed to date, this estimate is woefully low, experts believe.

Critics maintain that the government was slow to act from the start. The first confirmed SARS-CoV-2 infection in the US was reported on Jan. 20, and the government declared an emergency on Jan. 31. By Feb. 4, when the CDC launched its test under EUA, there were already 11 known cases in the US. And although it was known by mid-February a faulty reagent in CDC's EUA-authorized test would delay public health labs' ability to test patients, the FDA first declined APHL's request for "enforcement discretion" over LDTs, and then, on Feb. 29, issued a guidance easing the regulations to allow labs to validate and launch LDTs as long as they agreed to submit an EUA 15 days later.

It did not have to play out this way, said Javitt. "FDA didn't have to invoke EUA. These are LDTs. FDA could have exercised enforcement discretion for all coronavirus LDTs, or at least could have, from the outset, allowed labs to start testing while completing the EUA paperwork," she said.

Last week, in an effort to address test shortages in New York, the FDA exercised "enforcement discretion," allowing the New York State Department of Health to act as a third-party reviewer and approve tests developed by labs so they wouldn't have to submit EUAs to the federal agency. If anything, the Feb. 29 guidance and the actions it took with NYSDOH shows that the agency "had the power all along" to exercise enforcement discretion if it wanted, Javitt observed.

Impact of uncertainty

Although the FDA has a long history of exercising enforcement discretion over LDTs, the agency has tried to end that practice at times, with mixed results. It recognized as far back as the early 1990s that the lab industry was changing the way it was marketing tests, and it then sought to regulate research-use lab tests and even put out a rule on analyte-specific reagents used in LDTs and in vitro diagnostics. In the mid-2000s, the FDA again sought to unsuccessfully regulate lab tests using complex algorithms, because the agency wanted to ensure they provided patients accurate results. Starting in 2010, the agency shut down several lab tests sold directly to consumers online, until 23andMe reentered the market with an FDA-authorized product in 2015 and other providers found other legal workarounds.

By 2014, the agency tried to take a more overarching approach to regulating LDTs and bring all such tests under its aegis. It issued a draft guidance that was extremely unpopular with labs. The industry quickly hired lawyers to make the case that the FDA did not have legal authority to regulate lab processes. Ultimately, after significant feedback from industry players, the agency decided in 2016 not to finalize that guidance.

When the Trump Administration's newly minted FDA Commissioner Scott Gottlieb took the reins at the agency in 2017, he attempted to start afresh with the lab industry by making the case for a new regulatory framework which would be advanced with stakeholder input and through Congress. The bill that Bucshon and DeGette introduced earlier this month is largely drawn from a technical assistance document the FDA submitted.

This ongoing tussle between the agency and the lab industry contributed to an environment of uncertainty. For example, over the past year and a half, the FDA took action against labs providing pharmacogenomic testing without its approval, but industry players have said that this created an enormous amount of upheaval in the space because the agency wasn't transparent or consistent in its messages to labs.

Over the last 10 years, the FDA has leaned more toward enforcement instead of exercising discretion, said Karen Kaul, chair of the Department of Pathology and Laboratory Medicine at NorthShore University Health System in Evanston, Illinois. She recalled that during the H1N1 pandemic in 2009, the FDA did not crack down on labs that decided to launch tests. "We were actively testing [during H1N1] but over the past decade FDA has spoken more about enforcement," she said.

In contrast, during the Zika virus outbreak in 2016, when more than 5,100 cases were reported in the US, the FDA contacted Texas Children's Hospital and United Methodist Hospital after they announced they had developed a Zika test that could give pregnant women quick results in a hospital setting. In its letter, the FDA questioned why the hospitals were offering their test without premarket approval or under an EUA.

"The pregnant population really needed this information, but these labs were told to stop," recalled Kaul. "That sent a message and labs communicate with one another. So, back in January, we were all watching [coronavirus] unfold and wondering what to do."

Kaul's lab at NorthShore decided to launch an LDT following FDA's Feb. 29 guidance. NorthShore went live with its test last week and plans to submit for an EUA in coming days, as the guidelines dictate. In validating the LDT, Kaul's team matched its performance to the CDC's test, hoping "the process through the FDA would be easier," she said. "[The possibility of FDA enforcement] does affect our thinking in that regard."

The EUA provisions in the recently introduced VALID Act are similar to the policy FDA outlined for LDTs in its Feb. 29 guidance: validate and launch the tests, notify FDA, and submit the EUA at a later date. It can benefit the public in future pandemics to have this process codified in law, in Javitt's view, and spell out what FDA can and can't do in an emergency. "That way they don't have to reinvent the wheel every time," she said. "The bill's language sets an expectation about how a regulated entity will behave and puts an end to the confusion around whether the FDA will enforce or exercise discretion in an emergency."

Need for centralized authority

As NorthShore begins testing patients, Kaul believes the lesson that regulators should take away from this experience is not only the critical role hospital labs have in emergency situations, but also that LDTs are critical to the healthcare system at all times. "I would hope that the current situation, where hospital labs are being drafted to develop tests because we simply don't have the needed testing capacity, would influence regulators to realize that with appropriate guidelines and materials we can do an excellent job," she said.

In Kaul's view, whether LDTs for SAR-CoV-2 or for cancer biomarkers, labs sorely need reference materials for test validation and standards they can measure test performance against. The FDA would not necessarily have to get involved, but such standards and materials could be made available for proficiency testing through bodies like the College of American Pathologists and potentially other organizations.

"We do need some sort of regulatory framework to ensure high-quality work," she added. "Whether it's [done by] FDA, CAP or [through updating] CLIA will be battled out for a period of time to come … But the situation we're finding ourselves in does shine a bright light on the need for speed in certain situations." In the present crisis, labs are demonstrating their ability to provide rapid and accurate testing, Kaul added, and wondered whether, after this experience, it may be possible to advance such a simple path for all LDTs.

As regulatory hurdles are easing, laboratories trying to implement test kits or advance their own LDTs are having to deal with other challenges. These include insufficient expert personnel for operating tests and breakdowns in the supply chain limiting access to reference materials and reagents.

In Brooklyn, New York, Lenco Diagnostic Laboratories is among the 28 labs the NYSDOH will authorize to test for SARS-CoV-2. By marshalling the resources of all these labs, the city is hoping to push the daily testing capacity to 6,000 tests per day. However, according to Boorstein, who heads up oncology and esoteric testing at Lenco, the lab hasn't been able to start testing due to a reagents shortage. Some vendors have said they could supply reagents in a week, while others are backed up until May or June.

Lenco is planning to use research-use reagents from a major manufacturer (which he didn't name) to validate testing and migrate to an EUA kit when it becomes available. The lab is hoping to initially launch testing with the capacity to report 300 results per day, and eventually ramp up to 3,000 tests per day.

However, in Boorstein's view, loosening LDT regulations won't help labs with the issues they're facing now. "People are using this as a reason to bash the FDA and loosen the rules on LDTs," he said. "That's not really the problem [presented by] coronavirus."

The government's initial assumption, namely that the CDC and the state public health labs would be able to handle the volume of testing needed, seems in retrospect ill-advised. Nevertheless, Boorstein questioned whether opening up testing at the outset to LDT developers would have rendered a better outcome given the severe supply chain issues labs are now facing. "If a thousand labs try to set up LDTs, then all the resources would go toward a thousand labs trying to set up LDTs, and no one would have enough reagents to run the tests," he said, noting that the current challenges facing labs indicate the need for more centralization of authority and standardization.

What people seem to want, he opined, is the ability to go to their local hospital if they are feeling sick and get tested. If they're infected, they'd be hospitalized or isolated, and if not infected, they'd go home. That scenario will not be achieved with local labs developing LDTs that can do a few dozen or a hundred tests a day. Instead, it will require hospitals to conduct testing on high-throughput RT-PCR machines that can turn around several thousand tests daily, or on simple, rapid cartridge-based systems that can provide results in an hour or less. "These solutions have to come from the big manufacturers," he said.

On Friday, the FDA granted EUA to Roche for its RT-PCR cobas SARS-COV-2 test. The authorization allows hospitals and reference labs with cobas 6800/8800 systems to process 96 results in under four hours using a single machine and turn around 384 results or 960 results in eight hours using one cobas 6800 or cobas 8800 system, respectively.

"That's what we need. We don't need a hundred labs doing a hundred different tests all as batches, all slow and manual," Boorstein said. "We need high-throughput, rapid tests from major manufacturers to be made widely available as soon as possible."

The right time for new regulations?

Given all the challenges labs are facing, this may not be the right time to consider big legislation like VALID that would dramatically change the oversight system for labs, several policy experts said. "We have a strong nationwide lab testing infrastructure, and it's being put to the test," said SWHR's Miller. "We're going to have to study this [bill] and see what the implications are. There might be implications for reimbursement, manufacturing capacity, and what kind of protocols should be put in place to respond faster in these situations."

Miller recalled the diagnostics industry's experience backing a law, called Protecting Access to Medicare Act of 2014, which labs had hoped would stave off the unpredictable payment cuts Medicare was imposing on tests. However, Centers for Medicaid & Medicare Service's interpretation and implementation of the pricing law still resulted in deep payment cuts and did not align with what the lab industry believed the bill intended. The lab industry group, ACLA, ended up suing the government to try to strike down certain parts of CMS' final rule implementing the law.

"We saw through PAMA what happens when a bill isn't adequately thought through. There was contraction in the lab industry," Miller said. "If we push through a regulatory bill and it's overly burdensome, we might see contraction in the lab industry again."

The Association for Molecular Pathology, the College of American Pathologists, and ACLA are all reviewing the bill and putting together their formal responses. Labs have generally been wary that FDA regulations would slow down their ability to adapt to advancing science and public health needs. They have also feared the agency would impose duplicative requirements on top of those they have to fulfill for CAP accreditation and CLIA certification.

Peter Kyriacopoulos, APHL's chief policy officer, pointed out that public health labs are already a highly regulated group, and he has communicated his concerns to the FDA and VALID's sponsors in this regard. "We've been urging everybody to address those issues … so we don't have inspectors showing up and expecting different things, causing actions that are duplicative or at cross purposes," he said, adding that if these aspects can be worked out, then the APHL doesn't have a problem with FDA having a role in regulating lab tests.

However, Kyriacopoulos also observed that the coronavirus pandemic is absorbing a disproportionate amount of time from state, local, and commercial labs and occupying a lot of the resources within federal agencies. "I don't know who's left to do the work that would be required to fashion a legislative proposal that would be able to make it all the way through the process," he said.

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