For SARS-CoV-2, clearing the air on EUA tests

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July 2023—As the COVID-19 federal public health emergency drew to a close in mid-May, industry experts explained what will and won't change for the laboratory and weighed the fallout from the drop-off in SARS-CoV-2 testing.

Alesia McKeown, PhD, scientific partner at Roche Diagnostics, in mid-May addressed customer concerns that with the end of the public health emergency laboratories would be required to use only FDA-cleared SARS-CoV-2 tests or use the EUA product as a high-complexity test. "The end of the public health emergency does not impact ability to utilize EUA tests for continued diagnosis of SARS-CoV-2, regardless of complexity or CLIA categorization," Dr. McKeown says.

The Food and Drug Administration hasn't yet set a date for the end of the SARS-CoV-2 emergency use authorization, Adam Borden, senior vice president of policy and strategy at the American Clinical Laboratory Association, said in a May webinar hosted by Roche. The FDA will give at least 180 days' notice before the termination date, after which manufacturers will be permitted to continue distributing EUA test kits if the company sends a premarket submission to the FDA before the termination date. Laboratories will be allowed to use their stock of EUA test kits through the tests' expiration date even if the manufacturer hasn't sent a premarket submission to the FDA, he said. For now, the agency will continue to issue new EUAs, and laboratories can continue to order EUA test kits.

The FDA has not said it will publish where manufacturers are in the regulatory process, Borden said. "It's best to make sure you connect with your manufacturers to know where they are—if they've submitted already, what their timeframe is."

"But again, we don't have that EUA termination date yet," he added.

Roche is communicating closely with the FDA to support the transition for IVD clearance of its EUA products, Dr. McKeown says. "We are working to ensure that patients and our customers have access to the testing solutions they need to provide accurate diagnosis across the continuum of care, now and in the post-pandemic era."


Dr. McKeown

For laboratory-developed SARS-CoV-2 tests, following the EUA termination date the FDA will revert to its normal enforcement discretion policy for LDTs. This will include LDTs that have EUAs and new SARS-CoV-2 tests developed in the future.

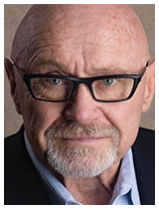
Daniel Rhoads, MD, assistant professor and section head of microbiology at the Cleveland Clinic and vice chair of the CAP Microbiology Committee, thinks the FDA might allow some SARS-CoV-2 EUA testing to continue into the future. “I wouldn’t be surprised if the FDA says, ‘There are a lot of options on the market and many manufacturers have moved to 510(k)—there’s no reason to maintain EUA because there are good solutions to meet the needs of the public that already have achieved full regulatory clearance.’ But I also wouldn’t be surprised if they said, ‘There’s a little bit of EUA still on the market, but it’s not causing any harm; the risk is low. We’re not going to push everybody to discontinue EUA testing.’” Diagnostic tests for the Ebola and Zika viruses and several others still are under EUA.

Dr. Rhoads expects the transition to IVD to be relatively simple for the laboratory. “If the chemistry and assay stay the same, and manufacturers are just getting a different regulatory mark, that should be straightforward. However, if there’s a need to optimize assay chemistry or remove an EUA indication like asymptomatic screening at the same or a similar time as changing the regulatory labeling, that will potentially cause confusion and be more challenging,” he says. “Specifically, laboratories will need to determine what changes, if any, accompany the updated regulatory labeling. If it is a fundamentally different assay, then it needs to be validated in vitro anew.”

“I don’t expect a lot of this to happen, but it might happen,” he continues. Cepheid is an example of a company that has updated its chemistry. “So there is precedent that manufacturers optimize their chemistry to keep up with the mutations and the viruses.” Other manufacturers, he says, have begun to receive FDA clearance for combination assays that never had EUA, such as the Hologic Panther Fusion SARS-CoV-2/Flu A/B/RSV assay. “Although the pace of change has slowed, we haven’t yet achieved a steady state,” Dr. Rhoads says. “Transitioning away from EUA and toward FDA-cleared devices will be a step toward a steadier state.”

As more manufacturers seek 510(k) clearance, they could see a slowdown at the FDA, says Larry Worden, founder and principal of IVD Logix, a market research and consulting firm. It won’t recall the early days of the pandemic, when the FDA was unable to accommodate any pending submissions other than EUA review, “but it’s going to be a challenge and everybody can expect longer regulatory approval processes.”

Companies that entered the market during the pandemic may put in a premarket submission for their EUA products but fail to make it through the full regulatory process. “If you have a submission in process, your EUA will not end. It’s an incentive to put something in, to extend your available marketing time,” Worden explains. Though the products may be well suited to a regulatory submission—“these tests were used at high volumes and gained a large experience base and potentially clinical data”—many of these companies lack the experience needed to navigate the regulatory process, he says. The difficulty isn’t in putting in the marketing submission; rather, “it’s doing it practically and doing it with the forethought of what’s going to be needed to see it through to the end.”


Worden

Some of the non-clinical companies that expanded into SARS-CoV-2 testing because of the immediate need, such as those in environmental testing or research tools markets, hoped to use pandemic revenue to broaden their offerings and compete in the clinical molecular PCR market. “A lot of the companies that received [SARS-CoV-2] emergency use authorizations were naive in terms of regulation and reimbursement,” Worden says. “They entered the market when the hurdles were low.” IVD Logix worked with a number of these companies to outline “the shape and size of the clinical market,” the test development challenges and other hurdles, and the expertise of the established companies, he says. “Some of them decided to give it a shot anyway and introduced themselves as broader line in vitro diagnostic companies, and they have not succeeded.”

Of the structure of the IVD industry post-pandemic, Worden says it’s the established in vitro diagnostic companies that ultimately are going to benefit. “We began to see consolidation even before the end of the pandemic, when a lot of the testing went back to the large manufacturers once they had the ability to meet demand.” The top 10 IVD companies typically represent about 65 to 70 percent of total global revenue, he says. “In molecular, if you look at just that segment, the top 10 represent about 90 percent, as a result of COVID.”

[dropcap]W[/dropcap]ith the end of the public health emergency, Medicare reimbursement for high-throughput molecular SARS-CoV-2 testing reverted from an enhanced rate of $75 plus $25 for results within two days to the standard rate of $51. ACLA’s Borden said in the Roche webinar that private payers will not necessarily be held to that price. The enhanced rate was for high-throughput standalone SARS-CoV-2 testing only; Medicare rates for multiplex testing have not changed, Borden tells CAP TODAY. “They could change from the private payer side, but that’s all negotiations between the provider and the payer.”

The enhanced rate for high-throughput testing, which early in the pandemic was set at a flat rate of $100, was critical to developing laboratory capacity and supporting the buildout of infrastructure, he says. “It was helpful on the innovation side, but also for growing capacity.” Borden expects testing capacity to remain strong among ACLA members, though some smaller laboratories may curtail SARS-CoV-2 testing. “We would have preferred to have the enhanced rate, to ensure that capacity.”


Borden

When the emergency was in effect laboratories were required to publish their SARS-CoV-2 testing prices, and payers were required to pay the published price if no other rate was negotiated. With the end of that policy, Borden says, some payers are communicating new payment rates for tests. “That’s something that is coming out of the end of the public health emergency.”

One policy that has not changed with the end of the emergency: The Centers for Medicare and Medicaid Services is allowing remote review of digital laboratory data to continue, without the remote testing site having to obtain a separate CLIA certificate. Remote review of physical slides is no longer permitted.

Initially, Borden says, the CMS indicated that only pathologists would be permitted to continue remote

review of digital materials after the emergency's end. On May 11 the agency extended its enforcement discretion for remote review to other laboratory personnel. "It's welcome news," he says. "And ACLA did advocate on that topic throughout the year."

Lisa-Jean Clifford, chief operating officer and chief strategy officer, Gestalt Diagnostics, calls the decision to continue allowing remote review "a turning point" for the digital diagnostics industry and says the regulatory bodies are "coming up to speed" in understanding the logistical differences between remote review of digital images and remote review of physical slides.

"The regulatory bodies understand and are acknowledging that there is no human tissue or human sample being reviewed remotely when digital images and workflows are being performed, so there is no need for an additional CLIA license or clean lab environment for remote reviewing and sign-out," Clifford says. With its decision the agency has sent a clear message on the path forward for digital pathology, she says. "People who have become accustomed to working remotely are going to continue to leverage digital, and those who have been doing their work on glass are going to be looking to replace that workflow with digital so that they can continue their remote work" now that glass slide review again requires a CLIA license or CLIA-licensed location.

The agency's decision to extend remote review to all laboratory personnel reflects a recognition of the value and role of digital pathology, she says. "Glass can get lost, be misplaced, and it can break. Tissue fades or changes in character from its original state over time. A digital image is always accessible—anywhere, anytime, and in its original quality—and will always reflect what the diagnosing pathologist saw at the time of diagnosis. All these points lend to the understanding that not only is remote digital viewing, workflow, and sign-out not a risk for anybody—patient or lab personnel—it provides clear advantages for both."


Clifford

For digital pathology, the pandemic accelerated what was already in motion, Clifford says, with remote work playing a significant role. "With digital technology and solutions available to make case review and sign-out a remote and automated process, remote review has become a natural extension to what we are seeing in every other industry for remote functionality." In the digital pathology space, technology development and remote working fostered an arena for innovation. "The focus and investment were not only on core digital diagnostic processes, but also on how to leverage this technology in an automated fashion—to have real-time access to people both within your organization and external to it for formal consultations or curbside conversations with colleagues, and to do so in a secure manner."

[dropcap]I[/dropcap]n the latter part of the pandemic, when supply chain problems settled, many laboratories brought in highly automated sample-to-answer platforms such as the Roche Cobas 6800 and Abbott Alinity m. "We saw a lot of the in-lab EUA testing shift from open PCR platforms or other platforms acquired to fill the demand and put on more automated, less hands-on and labor-intensive platforms," Worden says. "The laboratories I've talked to want to keep all these platforms that they can

because of the investment. It's a once-in-a-lifetime opportunity to expand their menu offerings with already realized sunk costs." Some labs may bring in tests previously sent to a commercial laboratory. "You might be able to do that at a lower test volume than you otherwise would because the economics are more favorable."

Point-of-care devices, too, purchased for SARS-CoV-2 testing, are being diverted for other testing like group A strep, influenza, and RSV. "They didn't have the ID Now or Roche Liat before, but now they've got it so they might as well use it," he says. For manufacturers, "the dynamic there is to look at what the next menu offering is or what the menu rollout is, to keep those instruments pulling reagents." Laboratories also have begun to shift from standalone testing for SARS-CoV-2 to multiplex testing for SARS-CoV-2 and the other seasonal respiratory viruses. "In a sense it's a transition to a more endemic environment, where you have those other assays that would be there regardless of whether there is demand for a standalone COVID test. It fits a testing model that is more viable in the long term," Worden says.


Dr. Rhoads

Dr. Rhoads, too, sees the field moving toward multiplex testing. "There are a couple reasons not to multiplex," he says, noting its cost and difficulty for some. "But more and more manufacturers are getting into the space, and to differentiate from other products on the market they're trying to multiplex better—cheaper, faster, easier, and more accurate." Considering whether the multiplex result will change patient care is important, he notes. "If it's not flu or RSV or SARS-CoV-2, most of the time, for most patients, all the other viruses are just all the other viruses. You can lump them together as a viral upper respiratory infection that we're going to manage with supportive care."

The Cleveland Clinic laboratory uses the Cepheid GeneXpert, the Hologic Panther, and the Roche Cobas 8800 for its SARS-CoV-2 testing. "We also use BioFire for a panel that includes SARS-CoV-2," Dr. Rhoads says. The laboratory has retired its SARS-CoV-2 laboratory-developed test. "Laboratories have migrated to manufacturers with IVDs that either have EUA, have 510(k), or have EUA and are moving toward 510(k). My expectation is there aren't going to be many labs that maintain LDTs and independent EUAs for SARS-CoV-2 because of how the market's changed. A lot of this is supply chain."

The laboratory still has EUA for a SARS-CoV-2-only and a SARS-CoV-2/influenza self-collection device, he says. "We have the EUA for the unsupervised self-collection of a sample, and then we pair it with Roche's EUA Cobas platform. So we have questions about what happens when Roche's platform gets 510(k): Can we continue using our EUA collection device with their 510(k) device?" If the laboratory should lose regulatory authorization for its self-collection device, "we're going to be able to maintain testing and patient care through other mechanisms," he says. "The need for the self-collected sample type is not as great as it was a couple of years ago."

Demand for asymptomatic molecular and antigen point-of-care screening—which the CMS allowed during the public health emergency despite screening being outside the tests' instructions for use—also has dropped. With the termination of the emergency, such tests will be considered high complexity

when used for screening. “I think demand for screening is going to be low in the future, and it’s low right now,” Dr. Rhoads says. “I’m hopeful that last winter is indicative of what we’ll see in the winter ahead, and last winter we didn’t see the omicron surge. The seroprevalence of spike antibodies is very high now. So the risks have changed, and where we are in the pandemic is different from where we were a couple of years ago.”

For the Cleveland Clinic laboratory, the pandemic became an opportunity to bolster operations. “Our molecular virology laboratory is now staffed 24/7, so we can do round-the-clock testing for analytes that we previously did only on first shift. And that enables us to provide better patient care with shorter turnaround times,” not only for SARS-CoV-2 but also for other viral testing and sexually transmitted infections. The laboratory also upgraded equipment to meet testing needs. “And now, as demand has waned for SARS-CoV-2 testing, we have the equipment and we’re trying to sort out the best way to use it.”

Says Dr. Rhoads: “I don’t expect every lab to maintain the workflow that was present at the height of the pandemic, but I hope where it falls back to is still a stronger state than it was before the pandemic, with more staffing, more equipment, and shorter turnaround times. I’m hoping we can maintain that.”

[dropcap]T[/dropcap]he laboratory at Dartmouth-Hitchcock Medical Center brought in higher-throughput instruments to meet testing demand during the pandemic, says Laura Tafe, MD, associate professor of pathology and laboratory medicine, Geisel School of Medicine at Dartmouth, and president of the Association for Molecular Pathology. A significant portion of the laboratory’s viral testing already was performed on a smaller automated instrument. “We’ve converted almost everything to the larger instrument,” Dr. Tafe says.


Dr. Tafe

New hires made to meet the demand for SARS-CoV-2 testing have been diverted to other assays and development work in other areas of the molecular diagnostics laboratory, which at the pandemic’s height ground to a halt. “One note of concern is whether our institutions will continue to support positions that were hired with COVID testing in mind. We now have to justify these positions for other uses in the laboratory.” In doing so, “I suspect there will be variability across institutions.”

The pandemic’s early delays in testing reinforced for Dr. Tafe the importance of laboratory autonomy. “The system failed a lot of people in terms of getting [testing] access quickly, and there were also challenges within the FDA and with the EUA process for laboratory-developed tests. For us it reaffirmed the need for laboratories to be flexible in developing these tests,” as did the need to accommodate variants.

AMP has for many years opposed mandatory FDA regulation of laboratory-developed testing procedures—the term it prefers to laboratory-developed tests—and advocates that oversight be through enhanced CLIA regulations, a proposal that evolved over the course of the pandemic. AMP surveyed laboratories on the EUA process during the pandemic, Dr. Tafe says. Results from that survey will

inform AMP's updated CLIA modernization proposal, "which will allow laboratories to demonstrate both analytical and clinical validity in a streamlined manner and the least burdensome manner."

For pandemic preparedness, AMP supports the formation of a laboratory response network, Dr. Tafe says. "We're asking for Congress to codify a laboratory response network that includes all types of clinical laboratories," she says. During the pandemic "a lot was put on the public health laboratories initially and there was underutilization of the academic and community laboratories for testing."

Other preparedness measures that AMP supports include a guaranteed allocation of resources to laboratories in the event of future supply chain failures and a surveillance plan to monitor emerging pathogens and variants. The organization also supports hazard pay eligibility for laboratory professionals.

AMP has suggested these preparedness measures be added to the Pandemic and All-Hazards Preparedness Act, which Congress must pass by Sept. 30 to reauthorize. "Congressional lawmakers have to readdress that this year, and these are some of the elements we're suggesting they look at or add."

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