Faced With Confusion, Questionable Claims, FDA Addresses Coronavirus Serology Testing

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NEW YORK – The US Food and Drug Administration held its third of now-weekly virtual town hall meetings Wednesday to clarify its guidance to developers of tests for SARS-CoV-2 infection.

Among the topics, the FDA announced that an inter-agency group has been formed to validate serology tests, and it addressed issues related to CLIA categorization of tests in the COVID-19 emergency. It also responded to a host of thorny questions regarding issues such as post-mortem testing, state issued test authorizations, 3D printing of devices, and test manufacturing. Overall, serology was the topic du jour.

The FDA now has two pathways for serological tests, as previously reported. The so-called "Policy D" is meant for blood tests that detect a patient's antibody response to the virus, which can indicate a current or previous infection. Under this policy, tests are allowed to be marketed in the US as soon as the manufacturer sends an email notifying FDA that it has completed a validation.

A pathway called "Policy C" is also open to serology tests. In this pathway, a manufacturer files an Emergency Use Authorization application, which potentially involves a more rigorous validation process. The agency said previously that this pathway could be for tests that are meant to be used at the point of care or for sole diagnosis of COVID-19.

Only one serology test – the qSARS-CoV-2 IgG/IgM Rapid Test from Cellex – has followed Policy C to date, while approximately 70 other serology test makers have notified the FDA of their intent to market their tests in the US.

However, "serology tests are growing in importance for our response to this emergency in order to aid the determination of patient immunity and prior exposure, and as a result accurate testing is very important," said Timothy Stenzel, director of FDA's Office of In Vitro Diagnostics and Radiological Health in the town hall.

The agency welcomes full EUA submissions for point-of-care and high-volume central lab serology tests, he said, adding that both of these are going to be necessary to address the upcoming need. Stenzel also acknowledged that there is as of yet no EUA application template for serology tests as there is for molecular tests, but the agency is working to create one.

Since the FDA began allowing serology-based SARS-CoV-2 tests to be marketed under policies C and D, some firms have launched their products with dubious claims about their regulatory status, which has caught the FDA's attention. The agency is trying to make it clear that firms that have gone through Policy D are not EUA authorized, and on Tuesday FDA Commissioner Steven Hahn issued a statement saying that "some firms are falsely claiming that their serological tests are FDA approved or authorized, or falsely claiming that they can diagnose COVID-19. The FDA will take appropriate action against firms making false claims or marketing tests that are not accurate and reliable."

Indeed, Stenzel said there has been some concern about sensitivity and specificity of tests coming into the US through Policy D.

As a result, "the FDA in collaboration with other agencies is standing up a voluntary inter-agency program to help address and verify accuracy," Stenzel said. Developers can participate voluntarily by sending their point-of-care test kits and any instrumentation that might be needed to a central lab for validation, and the agencies are putting together a panel of sera and plasma to independently evaluate test performance.

Stenzel encouraged any developers interested in this program to email the FDA. Also, "we are hoping that there will be enough remaining plasma or sera to develop panels that we could send to developers … At this point it is probably best to stay tuned – if there is such a panel, we will make that publicly known," he said.

He also reviewed the CLIA categorization of tests that have followed the different pathways that the agency has laid out.

Tests that receive EUA have been authorized for use in specific environments. For example, the Cellex serology test is for use in labs authorized under CLIA regulations to perform moderately complex testing. Tests that are authorized in their EUA for point-of-care are deemed to be CLIA-waived tests.

But, tests that have gone through Policy D have not been reviewed by FDA and have not received a CLIA categorization, and so they revert to highly-complex test status, Stenzel noted.

"It was not our intention to limit the use of rapid serology tests that are otherwise designed to be used in a point-of-care setting. However because of the limits that we have in law, it is the opinion of [the Centers for Medicare and Medicaid Services] that these can be performed in high-complexity labs," Stenzel said. He added that developers can choose to come through a full EUA authorization process so that a test can be deemed point-of-care and be allowed to be used in waived settings.

The agency is also looking at "potential alternate pathways to achieve the same end," Stenzel said, including its interagency test performance evaluation. "We may have a

pathway open … that we're looking at, and we encourage all serology point-of-care developers to participate."

Stenzel followed up to say that the agency may not yet have made clear that point-of-care tests marketed under Policy D are considered high-complexity tests, as there are two related posts on its FAQ page. "We'll try to resolve the confusion on the website," he said.

He did note that Policy D serology tests validated for capillary or finger-stick blood samples could technically be performed in high-complexity CLIA labs. "A high-complexity lab could set up a finger-stick station to be able to do these tests under their high-complexity certificate," Stenzel said. To be deemed CLIA-waived tests, however, makers of point-of-care tests must proceed through Policy C and apply for EUA.

Other thorny topics

With much about SARS-CoV-2 still unknown, and policies around testing for the coronavirus still a work in progress, Stenzel also implicitly acknowledged the confusion that many test makers may be facing. He emphasized that the agency's Frequently Asked Questions page is continuously being updated with specific guidance.

For example, regarding validating other transport media, swabs, extraction reagents, and PCR instruments, Stenzel reiterated that labs with their own EUA, or ones using EUA devices or products, can do a bridging study and do not need to submit an amendment or application.

"However, in both situations we would love to see the validation data that you've generated in order that it might be helpful to others, and with your permission we would like to add the alternate supply or reagent onto our Frequently Asked Questions page," he said.

In contrast, commercial test manufacturers that alter their products require validation and a submission to the FDA, "usually in the form of a supplement," Stenzel said. "We will also work closely with you to address those additions as quickly as possible to make more options available."

Stenzel also spoke about an area that has generated a lot of interest in the SARS-CoV-2 testing space, but which has created some controversy and questions – home-based testing. In the past month, a number of companies have launched, or said they would launch, such tests. Last month, the FDA issued an alert to warn consumers to be on the lookout for such tests that may be making unproven claims.

Stenzel emphasized on Wednesday that home testing and home collection require EUA. "If you are interested in this pathway, please reach out to us at our general EUA address and we'll work with you to design the appropriate studies to ensure that home collection is safe, and is accurate, and that the shipping return to the laboratory is also considered and is validated … and false negatives are avoided," he said.

There are six states currently authorized to review testing: Connecticut, Maryland, Mississippi, Nevada, New York, and Washington state, but "even if your state is willing to

authorize tests within your state, you are always welcome to submit an EUA application to the FDA," Stenzel said.

In the question-and-answer segment, a developer asked whether or not states can essentially override guidance against at-home serology testing by enabling at-home sample collection with samples mailed to labs. "We would ask that developers of home-use tests reach out to the FDA, and then if there is something that a state may be willing to do we can interact with that state to make a decision," Stenzel replied.

The FDA has, to date, authorized certain sample types, namely nasopharyngeal swabs, mid-turbinate and nasal swabs collected by a provider, or if self-collected in a healthcare environment, pharyngeal swabs, and sputum.

"We have seen some data with regard to a tongue swab, and there are parties interested in saliva," Stenzel said, adding that "some of these alternate samples may not perform as well as others, so at this time we would like to engage with the developer on an alternate sample type if it is not one of the ones that we have already authorized."

If, on the other hand, a developer wants to add or switch to another authorized swab or sample type, "you can perform your own bridging study if you are [a laboratory-developed test] developer, or if you are altering an EUA-authorized test, and you don't need to submit that to the FDA," Stenzel said.

Bridging studies could also be used by labs with EUA for an LDT to validate cadaveric samples, he said, noting that the agency has previously authorized an Ebola test for samples from deceased patients to confirm disease status and to protect others during mortuary practices.

In general, labs can use research-use-only components and instruments in COVID-19 LDTs, but Stenzel also clarified that manufacturers can develop kits for use with RUO instruments.

"Typically, outside of an emergency situation, we would require more work for an RUO instrument; however under the emergency authorization program, we will work with developers and manufacturers to validate those instruments, as well," he said. A molecular diagnostic kit maker could follow Policy C, validate and make available a test on an RUO instrument and file EUA within 15 days, and then "as long as everything looks good, we're good," Stenzel said.

He did, however, add that someday, when the emergency declaration comes to an end, there is a provision that allows for devices to be removed from EUA and require full submission. "There are potential pathways, it's just good to talk to the FDA ahead of time and be prepared," he said.

Regarding subsidiaries of the same company that are making the same test but at different manufacturing sites, using raw materials sourced from different places, Stenzel said only one EUA could suffice, or one entity could refer to data in the EUA of the first and "basically submit a shell," but this would need to be confirmed.

Finally, a laboratorian calling from Puerto Rico noted that there has been a shortage of molecular testing there that has been coupled with a flood of imported serology tests. Serology tests were sold and used by labs in Puerto Rico prior to FDA's guidance on serology tests issued March 16, he said. To determine whether patient results were obtained on permissible tests, it would be beneficial to know the exact date the manufacturer of each test in Policy D notified FDA, which is information not currently on FDA's FAQ page.

Sara Brenner, associate director for medical affairs and chief medical officer at FDA, emphasized during the meeting that FDA is working with its partner agencies to quickly figure out "essentially which serology tests will be best, with the realization that many have already been rolled out."

Brenner also commented on 3D printing of devices and other non-traditional manufacturing methods to address supply chain issues. She said that the FDA has formed a partnership with the US Department of Veterans Affairs Innovation Ecosystem, the National Institutes of Health 3D Print Exchange, and America Makes to share data and coordinate on open-source medical products for the COVID-19 response.