

Virtual Town Hall #88
June 29, 2022

Moderator: CDR Kimberly Piermatteo

CDR Kimberly Piermatteo: Hello and welcome everyone to Virtual IVD Town Hall number 88 for SARS-CoV-2 test developers in which we'll discuss and answer your questions about diagnostic tests in response to COVID-19. Thanks for joining us today. This is Commander Kim Piermatteo of the United States Public Health Service, and I am the Education Program Administrator within the Division of Industry and Consumer Education in CDRH's Office of Communication and Education. I'll be your moderator for today's Town Hall.

Our panelists for today's Town Hall are Dr. Timothy Stenzel, Director of the Office of In Vitro Diagnostics, which is also referred to as the Office of Health Technology number 7 or OHT7, in CDRH's Office of Product Evaluation and Quality. Joining Tim today is Toby Lowe, Associate Director for Regulatory Programs in OHT7, and Dr. Kristian Roth, Deputy Director of the Division of Microbiology Devices, also in OHT7.

For today's Town Hall, we'll begin with opening remarks, followed by answering your previously emailed questions, and then proceed to address your live questions.

A recording of today's Town Hall and transcript will be made available on CDRH Learn under the section titled Specialty Technical Topics and then the subsection titled Coronavirus (COVID-19) Test Development and Validation Virtual Town Hall Series.

The June 15th IVD Town Hall recording and transcript have been posted.

The next scheduled IVD Town Hall will be on Wednesday July 27, 2022 from 12:05 to 1:00 PM Eastern Time. Please refer to the Virtual Town Hall Series web page to keep up to date on upcoming IVD Town Halls via the link provided at the bottom on the slide.

And lastly, as a friendly reminder, to avoid any technical issues while participating live in today's Town Hall, please be sure you have joined the Town Hall via the Zoom app and not through a web browser.

At this time, I'd now like to turn it over to Tim, who will provide today's opening remarks. Tim, the floor is yours.

Timothy Stenzel: Thanks, Kim. And good day, everyone and glad you could join us today. As we reflect over the last two and a half years of the COVID pandemic, I'd just like to note the tremendous progress we've made in testing. The office has seen a deluge of submissions, and supplements, and amendments - authorized going on or approaching 500 unique test authorizations and over 1,000 supplements and amendments. And it's really-- all this success is a testament to all the developers that have been working so diligently, as well, over these last two and a half years and, of course, our brilliant and dedicated FDA staff.

So it's still sobering, as we're still seeing over 100,000 cases officially reported every day for COVID. And the death rate is ticking up a little bit. We're approaching 400 deaths a day again in the U.S. So we are

remaining diligent and vigilant here at the FDA, as I know you are, too. So thank you to so many of you who have been collaborators and partners with us in that.

My first formal opening remark-- that was just making note of where we are-- is not actually for COVID. We all know that there is an emerging disease worldwide, and in the U.S. And this call isn't typically reserved for anything other than COVID. But it is an emerging and important pathogen that the FDA has been vigilant early on and working very hard with many stakeholders inside and outside the government to make sure that our response to this emerging disease of MPV, otherwise known as monkeypox, is hitting the appropriate marks.

So just wanted to remind you all that monkeypox, or MPV, LDTs are under the usual FDA enforcement discretion for LDTs. And also, I just wanted to note that the FDA has been working early and hard to increase the availability and testing throughout-- and throughput-- of the FDA cleared CDC NVO kit. That kit was cleared many years ago and has been used in and scores of the public health labs around the country. The number is steadily increasing and is around 80 labs right now.

We're also expanding that testing into five major clinical reference labs. So the kits have already been made available to these five labs as of last week. And they're preparing to set up testing in their labs. And currently, the public health labs throughput per week is about 10,000 tests per week with the addition of the five major reference labs. And this is LabCorp, Mayo, Quest, Aegis, and Sonic. They volunteered among the large reference labs to proceed with this. And we expect that, eventually, over the next coming weeks, that they'll each be able to ramp up to a capacity of at least 10,000 tests per week. So that does take us to about 60,000 tests per week in the U.S.

That does cover all of the known and thought of mimic lesions that occur weekly, at least that are submitted for testing weekly. Those other mimic lesions can be herpes lesions and varicella lesions, as well as, occasionally, syphilis lesions. And so we've worked diligently to expand the capability for testing, and we'll see the fruits of that very clearly here in the coming weeks.

That's enough on monkeypox. This call is typically reserved for COVID, and we like to keep it that way. But I thought those were important announcements to make.

Moving on to COVID. So looking at the omicron prevalence and the impact, I wanted to discuss the impact on our current EUA recommendations for validation for antigen tests. We had seen, early in the omicron era, that it looked like antigen tests were seeing a decrease in sensitivity. That's been posted on the FDA website for months now.

And the data has continued to accumulate that it is not as sensitive. And so it's very important that we've been able to evaluate tests to date, at least, for their sensitivity for omicron so that users, clinicians, patients understand what the performance is for omicron. And we've seen the need, even for symptomatic patients, to require in the authorization serial testing because of the decreased sensitivity.

And so we have looked at the increasing prevalence of omicron. And we were looking at a prevalence that reached a threshold of at least 99% over the entire country. And that date that we've established is March 1, 2022 looking at the sequence databases. So as of now, any antigen clinical studies that were begun on or after March 1, 2022, will no longer need to prospectively collect sequence and sequence samples for their FDA. We're no longer recommending that for the submissions for antigen tests.

So therefore, if your antigen clinical study began on or after March 1st, there's good evidence that all positive samples are essentially omicron and we will not expect you to include sequencing data in your submission nor be automatically asked to provide it after EUA authorization.

We do continue to recommend that you bank your clinical study samples for potential further analysis, which could include sequencing at a later date, should circumstance warrant it. How could that warrant it? If mutations occur in sub-lineages of omicron that suggests further impacts on performance, we may need to do that. So please bank those samples.

So if your antigen study began prior to March of this year, we do recommend 30 confirmed and sequenced omicron positive samples prior to authorization as the FDA is seen, as I said, a significant drop in antigen test sensitivity for omicron.

OK, so with those remarks, I think we can move on to the previously submitted questions and our responses to them. Back over to you, Kim.

CDR Kimberly Piermatteo: Great. Thank you, Tim. Alright, we will now answer your previously emailed questions about COVID test development and validation. Please note, we have received some questions that were too detailed or test-case specific that we will not address today. For those questions, we will try to send a response in writing within a few days. If you have submitted a question and do not hear it addressed today, please look for a written response. If you do not receive a response within a few days, please feel free to reach back out to the CDRH-EUA-Templates@fda.hhs.gov mailbox for an update.

Tim and Toby will be addressing today's previously emailed questions. So for the first question, I'll be directing it to Toby. Toby, the first question is, is a human sample control required for a molecular-based OTC test? And if not, what other options would the FDA recommend test developers take to mitigate for improper collection?

Toby Lowe: Thanks, Kim. So generally, FDA recommends including an internal process control and, ideally, a human specimen control to ensure that an adequate sample was taken. Tests without a human specimen control should use a well-established collection procedure, such as a nasal swab placed into a buffer tube.

This type of workflow is well-established, and this has been shown, among other places, in the adequacy of nasal self-swabbing for SARS-CoV-2 testing in children study that demonstrated that even young children are capable of collecting an appropriate nasal swab sample. Other types of samples or sampling protocols should be discussed with FDA to determine whether a human specimen control is recommended.

CDR Kimberly Piermatteo: Thanks, Toby. Our second previously emailed question I'll be directing to you, Tim. Tim, the question is, has there been any further research to validate throat swabs for at-home COVID-19 diagnostic tests?

Timothy Stenzel: Yes, there has been some research. And unfortunately, the preponderance of evidence does not support adding this, in general. We have not authorized it. But I'll go on to say that we're open to it.

I would like to add that the CDC still recommends that throat swabs be collected only by trained health care provider. I'd also like to note that the NIH RADx program has assessed throat swabs for COVID, particularly for antigen tests, and the data did not support the addition of throat swabs.

So as I said, the FDA is open to the possibility of self-collected throat swabs, or physician, or health care worker collected throat swabs for rapid tests-- molecular and antigen, or even central lab tests-- if there is sufficient data demonstrating that the safety concerns have been addressed and that the swabs perform adequately according to our expectations of performance. But we have not seen this yet.

And as I said, there is this evidence that it doesn't appear that the benefits-- potential benefits-- would outweigh the potential risks, particularly for self-collection. But again, we're open to it. So the FDA currently still believes that the nasal swabs likely remain the best option for most tests and developers that adequately mitigate some of the risks.

And we do encourage developers continue to validate nasal swabs along with any other sample type that they are interested in pursuing. So if they're interested in pursuing a throat swab, then we would still recommend-- to mitigate your development risk-- that you include nasal swabs in your study. Back to you, Kim.

CDR Kimberly Piermatteo: Thanks, Tim. So the next few questions I'll be directing towards you, Toby. And our next question is, is it appropriate to conduct electromagnetic compatibility, or EMC testing, for our platform according to the IEC 61010-1 standard as discussed in the recently issued "Electromagnetic compatibility (EMC) of Medical Devices Guidance," instead of the IEC 60601-1-2 edition 4.0 from 2014 that is discussed in the EUA template?

Toby Lowe: Thanks, Kim. Yes, as stated in the "Electromagnetic Compatibility (EMC) of Medical Devices Guidance" that was just published earlier this month, on page 10 it states that most laboratory equipment and in vitro diagnostic devices (IVDs) are outside the scope of 60601-1-2. At the time of issuance of the EMC guidance, we do partially recognize the IEC 61326-1 2020 and IEC 61326-2-6 2020 and recommend using the test methods from these standards.

However, we also recommend using acceptance criteria specific to the device's functions and intended use and recommend using test levels specified by 60601-1-2 or alternatively determining the reasonably foreseeable maximum levels of the electromagnetic phenomena in the device intended use environments, such as through study of published literature or environmental measures. And it does appear that you could use 61010-1 to test your point-of-care platform for safety.

So we would recommend that you supplement this with a risk analysis that incorporates risks due to electromagnetic interference and electrostatic discharge. And if you have specific questions about your specific testing approach, we would recommend that you submit a Pre-Submission or pre-EUA to discuss that specifically related to your situation.

CDR Kimberly Piermatteo: Thanks, Toby. Alright, our next question is a CLIA certificate required for a lab conducting validation studies, including analytical and clinical studies for a COVID-19 diagnostic device, when there is no patient-specific result being reported to study subjects or to public health authorities?

Toby Lowe: Thanks, Kim. So from the FDA perspective, for high- or moderate-complexity tests, we do not have any issue with the analytical and clinical studies being performed in a non-CLIA lab, provided

the results are not returned to the patient or provider and the laboratory is able to perform the testing according to an appropriate study protocol. If there are specific questions about whether something is permitted under CLIA, we recommend that you reach out to CMS to discuss that.

And it's important to note that for point-of-care tests, we do continue to recommend that clinical studies be done in a true point-of-care clinical setting with the intended user, meaning a minimally trained user performing the testing as part of that study. Back to you, Kim.

CDR Kimberly Piermatteo: Thanks, Toby. This next question has two parts. The first part, or first question is, when does the FDA require automatic test result reporting for molecular OTC tests? The second part is, for an OTC device where a test result is always made available to a mobile application-- for example, a user can access the test result only through the mobile application-- should the mobile application report the result to public health authorities without a separate input from the user?

Toby Lowe: Thanks, Kim. So we'll address these both together. So for over-the-counter test, we do typically include a condition of authorization that requires developers to provide a diagnostic data capture and transmission solution to facilitate reporting of results to public health authorities and health care providers. The EUA can be issued without that reporting solution having been implemented, and that's when it would be included in a post-authorization condition.

And so generally, we work directly with each sponsor on how to best accomplish this, which may include automation of data capture and transmission, digital interpretation or reading of test results-- which would be accomplished using software as a medical device-- or digital health tools that reduce the user burden with regard to data collection.

And these solutions may be offered as an integral part of the diagnostic workflow, for example, an automated solution, or made available to the user voluntarily. Solutions that improve data quality and reporting as well as improve the user experience are strongly encouraged. Back to you, Kim.

CDR Kimberly Piermatteo: Great. Thanks, Toby. Alright, our last previously submitted question is, to support EUA for an OTC SARS-CoV-2 antigen test, does the FDA require a minimum percentage of low-positive samples collected in the clinical study?

Toby Lowe: Thanks, Kim. So in order to support the EUA authorization for over-the-counter SARS-CoV-2 antigen tests, we generally recommend that a developer evaluate a minimum of 10% low positive samples. Low positives are typically defined as samples in which any gene target is within three cycle threshold (CTs) of the mean CT count at the comparator tests LoD. This information can be found in the main antigen diagnostic test EUA template on page 28.

And it's important to note that we do want to see all of the data collected in your clinical studies provided in your EUA request, not only the first 10% low positives. Back to you.

CDR Kimberly Piermatteo: Alright, thank you, Tim and Toby. That wraps up the previously submitted questions. We will now move to take your live questions. To ask a live question, please select the Raise Hand icon at the bottom of your Zoom screen. When you are called on, please follow the prompt in Zoom and select the blue button to unmute your line. Then identify yourself, and ask your question. Please remember to limit yourself to asking one question only. If you have an additional question, you

may raise your hand again to get back into the queue. And I will call on you as time permits. And please remember, we're not able to discuss specific submissions under review.

Our first live question is from Sam. Sam, I have unmuted your line. Please unmute yourself and ask your question.

Sam: Yes, thank you, Kim. So we are always appreciative of all the work that the FDA is doing. And I'm just wondering right now in terms of the workload, and the bandwidth, and the allocation of resources to various programs in terms of priorities and others, and related to that is, I wonder if you track the average approval-- review and approval-- time right now for an antigen OTC test. Is there an estimate of how long it might take?

Timothy Stenzel: So that's hard to predict. That particular group has been hit hardest with submissions. And as always, as we said before, submissions that are complete, are easy to read and interpret, contain all the elements that we need to see, such as the studies-- the specific studies as to how they're performed and all the data-- and formatted in a way that's easily digestible by the FDA. And if we don't have significant major questions or concerns, that really speeds the review of those tests. You can always reach out to—

Sam: Is there anything, like an average, for all the various submission types, including complete ones and maybe some others?

Timothy Stenzel: I don't have that. We've authorized them in as little as one day this year for tests that were in the ITAP program. All those studies are done per FDA design under direct control of an NIH. And we see the data enrolling, and so we get exactly what we expect. We see the data, and we can make that decision with good certainty and quickly.

But if there are issues with the study design, if there are issues with the data, if there's unanswered questions or unprovided information, it really slows the team down. And we are engaging-- someone's been assigned a reviewer. You're being reviewed. And they're swamped.

And if they have questions, they've got to put together a complete list of questions. And then they go to you for that. So if you do feel that it's going on too long, you can always send me an email. Just send it to the templates email box and ask that your question be directed to my attention.

Sam: Got it. Thanks, Tim. Appreciate it.

CDR Kimberly Piermatteo: Thanks, Tim. Let's go to our next question. Our next question is coming from Wenli. Wenli, I have unmuted your line. Please unmute yourself and ask your question.

Wenli: Thank you very much. This is a Wenli Zhou from XYZ Laboratory. Thank you all very much for the hard work. And I have a question. Tim mentioned about the decrease the sensitivity of the omicron antigen test on the omicron. Just wondering, is that because of the higher percentage of low positives right now we see, as Tim mentioned in the previous Town Hall meeting, or there are any N protein mutation caused this decreased sensitivity?

Timothy Stenzel: We have seen a huge increase in the percent of low positives in taking and seeing all the data and clinical studies from even towards the end of last year compared to the beginning of this

year. So instead of seeing the usual 10% to 20% low positives that we had been seeing in typical studies prior to the end of last year, which reflects our template recommendations for low positives, we saw a jump to 30% to 40% low positives. And the higher the CTs go, the less likely antigen tests are going to be positive.

And so when you have 40% low positives in areas that really challenge antigen tests, then you're going to see a really big hit in sensitivity. Basically, it could be down to 60% sensitivity for antigen tests for a single test in symptomatic patients.

And we know that it's even more challenging for antigen tests to detect asymptomatic patients. So that performance is even lower than that. And it's why many of the recent authorizations have prescribed serial testing for symptomatic individuals and continued serial testing for asymptomatic individuals, as well.

It's important to note that, now, what's actually driving that is less clear. I don't think we have enough data to say it. Some of the early data we looked at-- vaccination status and potentially previous infection status, and that didn't necessarily reflect that. So there could be other-- there's continuing research into some of the other mechanisms for the lower sensitivity.

Some of the hypothesis out there is a lower anti-protein per-- as the ratio of the RNA present in the virus. And perhaps that changes through the natural history of an infection. And at the time when you want to perform an antigen test, there may be an under-abundance of anti-protein in the viral sample compared to RNA. Anyway, lots of questions, not as many answers, but clear observation of a significant increase in the number of low positives.

Wenli: Great. So in this case, when developers submitted their application, we've got some questions from people when they see their sensitivity is so low-- lower than the recommendation template. They don't know what to do, whether to submit, or to get more data, or-- they're kind of in the middle if they don't meet the requirements of the template.

Timothy Stenzel: Yeah. Well, if you look at some of our recent authorizations, you'll see that we do modeling to look at what is the performance down to, say, only 10% low positive. And we've provided some instructions on how to consider that. We just-- I think it's probably worthwhile, if you have observed a high percentage of low positives that you go ahead and submit all your data. We don't want to see just the first 10% of low positives in your data set. We want to look at the whole data set.

And we'll examine it and see if some of our work in modeling can't adjust for this. Because we're basically trying to make reviews this year equivalent to reviews that we did last year when there were only 10% to 20% low positives. We think very likely, if not with great certainty, that tests that we authorized prior to this year-- antigen tests-- if they faced 30% to 40% low positives, they would probably be subject to the same challenges.

And so we are trying to use modeling to match performance as we saw last year and as we expect this year for otherwise good tests. It's challenging. And it is one of the reasons why it's taking a little bit longer, now, to review antigen test applications.

Wenli: Got it. I see. Thank you so much.

CDR Kimberly Piermatteo: Thank you, Wenli. Thank you, Tim. We'll move on. Our next question is coming from EDP Biotech. EDP, I have unmuted your line. Please unmute yourself and ask your question.

Eric: Thank you this. Is Eric Mayer from EDP Biotech. First, we appreciate all of the dialogue with the FDA and the ability to ask questions and receive feedback. That's super helpful for developers.

My question is are around selecting an appropriate high-sensitivity RT-PCR comparator method. We received some feedback yesterday that there's some new current guidelines as to the threshold to be considered appropriate as high sensitivity. And I was wondering if you could detail what that sensitivity threshold now is in NDU per mL so that we can make an appropriate selection for comparator and discordant analysis.

Timothy Stenzel: Yeah, the best way to determine whether or not the test you've chosen is an appropriate comparator is to reach out to the FDA review staff or go through the templates email to ask if the test that you're thinking about using is an appropriate high sensitivity comparator. We do use a combination of criteria to assess and determine whether a test is high sensitivity or not. The NDUs are one input, but they're not the sole input.

We also consider tests that have-- molecular tests-- that have been validated on actual patient samples versus only contrived samples. So we still have some tests on the market that didn't use actual patient samples for their validation. So it's not a straight, cut-and-dry answer. And therefore, we haven't posted that information.

Plus, we always want to reserve the right to adjust that as needed and as new information becomes available. We have very limited data for most of the EUA-authorized tests. We don't have the full clinical study data that we would expect for a full authorization for most of the tests.

Therefore, we are faced with difficult decisions on deciding just which tests are the very most high sensitivity. But the FDA staff can assist you in making sure that you make the correct selection. That's important because if you don't make the correct selection, we may not be able to use the clinical study data that you generate to make an authorization decision.

And that's also another reason why we strongly recommend banking residual material, if possible, from the comparator test collection so that if additional testing on those bank samples could be helpful to a successful submission, you have those ready to be used.

Eric: OK, thank you so much. We'll reach out on email for the specific method we'd like to select.

CDR Kimberly Piermatteo: Great. Thank you, Eric. Thank you, Tim. Our next question is coming from Dennis. Dennis, I have unmuted your line. Please unmute yourself and ask your question.

Dennis Shay: Thanks, Kim. So my question is specific to molecular OTC use but in clinical studies. So as requirements to provide evidence of COVID testing in general continue to be loosened and thus the need for asymptomatic testing decreases, has the FDA been open to clinical studies incorporating callback or other enrichment studies to help reach asymptomatic endpoints?

Timothy Stenzel: Yeah. So I mean, to do an asymptomatic study now or in the past-- I mean, we're still seeing a lot of disease. And we know there's asymptomatic spread. It may, with vaccination and

previous infection, it may be increased. We don't know, with asymptomatic spread, what the level it's really occurring at.

I would say that asymptomatic screening is still an important tool for our public health response. The FDA is totally supportive of that. And we do, at the same time, we do realize the challenges of performing an asymptomatic clinical study. And so I'll answer your question specifically first, but then I'll also relay some work that has been long in the making-- a collaboration between the FDA, NIH, and the University of Massachusetts.

So we are open to methods of enriching for certain populations when a situation either is demonstrated is challenging to complete the study without enrichment, and in particular, with asymptomatics it is, if you're doing your own study, it can be very challenging. We've crunched the numbers all which ways, depending on prevalence of symptomatic disease or at least test positivity, and the study designs can be quite large and quite challenging to perform, let alone the costs involved in doing those studies. One of the estimates was that we might need-- a developer might need 10,000 patients in a study to get 20 positives. And it's probably lower than that now, but I doubt it's lower than 4,000 or 5,000 patients to get 20 positive asymptomatics. So that's just the challenge.

And so we've always been open, in the asymptomatic studies, to enrichment. It is important to do it in a way that mitigates and limits bias so that we do have a good understanding of the actual performance of the test and that it isn't biased in a way that would alter our understanding of the performance and, therefore, the understanding of potential users of such a test on the performance in the asymptomatic population.

I'll take a few minutes now to describe the study that was been ongoing since last year. It is a serial testing study involving both molecular tests and --EUA-authorized molecular tests-- and EUA-authorized antigen tests. And we'll be rolling out more details in the future of this study. But the study has been completed. We're analyzing the data now.

The purpose of this study was to collect information that could be generalized about, in particular, screening asymptomatic individuals for detection of SARS-CoV-2 and what it would take-- is one test sufficient, or are multiple tests needed for antigen tests? We have an overlying study design that can be also used to examine a molecular test.

We also have wanted to find ways to generalize this information. The study data is intended to be made for use by any developer. The study sponsors have rightly agreed to give right of reference to this data. So we're hoping, that at the very least for antigen tests, potentially and likely for molecular tests, that the data generated in this study can be used by all developers as long as they meet certain other sensitivity criteria. More to talk about that in the future.

But we have not recommended that, say, over-the-counter tests and any tests that had a post-market commitment of doing an asymptomatic screening study-- we have not recommended that they go ahead and start those studies. They are free to do that. They're free to do those asymptomatic studies. We get an occasional inquiry. They'd like the FDA to bless those designs.

We're not really encouraging that right now because we're hoping that this one, large study done on multiple EUA-authorized antigen and molecular tests will be able to provide the data needed to fill those

post-market commitments for validating a serial testing screening claim. Hopefully that information has been helpful to you.

Dennis Shay: Incredibly helpful. Thank you so much.

CDR Kimberly Piermatteo: Thank you, Dennis and Tim. Alright, our next question-- and I am going to apologize ahead of time for the pronunciation. But it's Venkateswaran I have unmuted your line. Please unmute yourself and ask your question.

Kodumudi Venkateswaran: Thank you, Kim. Thank you very much for having this Town Hall Series and providing opportunity to ask questions. My name is Kodumudi Venkateswaran from Tetraco. Thanks for Dr. Timothy Stenzel providing opening remarks in addition to the SARS-CoV-2 update about the monkeypox virus status.

My question is, in addition to the testing volume that you mentioned, maybe around 50,000 tests per week or so in the public health labs and reference labs, do you think there are going to be a need and opportunity for on-site or point-of-care molecular or rapid antigen tests for monkeypox virus? What are your thoughts?

Timothy Stenzel: So ideally, we would have such tests cleared. Obviously, such tests, in any outbreak situation, would be incredibly valuable. It's hard to tell which of the potential pathogens that could attack us next as a world and as a country would need FDA clearance or authorization prior to such an outbreak.

The numbers of patients infected in the United States is still, I believe, in the 200s. We're not taking that lightly. Those are confirmed cases. As we expand testing, we don't know what's going to happen with regard to confirmed cases. They may increase. How much they may increase is unknown. This is clearly an international disease, and we're clearly seeing how travel contributes to cases within the United States.

Developers, traditional kit manufacturing developers, are freely welcome to develop kits and come through the FDA full authorization process. That would-- because the CDC test has already been cleared-- 510(k) FDA cleared-- follow-on assays would be 510(k)s. But that's a lot of work with very little samples. So that is a challenging path for most developers to pursue right now.

And there has been some concern that you have to do vigorous swabbing to get a nice molecular result, clear molecular result. So I'm not sure how an antigen point-of-care test would perform on such a lesion or lesions. But you and anyone else are welcome to try to develop a test that can come to the U.S. market. You know there is quite a bit of development resource commitment and risk that this may not be-- that this may not warrant that development.

So Jeff Shuren and I have made certain recommendations and published those thoughts in a number of different publications about how a country might best prepare for a future outbreak. And we do believe that preparation can help.

I know that there are discussions about what to do beyond the current response of the CDC-- the CDC test, both in the LRN labs as well as in the commercial labs. And so I know that the U.S. government is

looking seriously at all these options and discussing them. And we want to try to stay ahead of any needs here.

Kodumudi Venkateswaran: Thank you.

CDR Kimberly Piermatteo: Thanks, Tim. We'll move on to our next question is coming from Don. Don, I have unmuted your line. Please unmute yourself and ask your question.

Don Cooper: Thanks, Kim. My name is Don Cooper from Neurogenics. And we have a clinical trial going on assessing antigen tests-- rapid antigen tests-- that has IRB approval. I think in the past, Tim, you had mentioned that IRB approval is not required for EUA submissions. Is that correct?

Timothy Stenzel: We don't-- it's not a review issue for the FDA. We do recommend you follow all federal, state, and local laws and regulations though.

Don Cooper: Right.

Timothy Stenzel: But it's just something that we review. I will say that following GCP-- good clinical practice-- for regular submission to the FDA is part of our review, and it can be a review issue—

Don Cooper: Understood.

Timothy Stenzel: --because consent regulations and guidance has been updated, I think, in 2018. And so that shouldn't hopefully come as a surprise to any developers about that. But as far as COVID EUAs, that's our current policy.

Don Cooper: OK, understood. When there's a change-- like after March 1, there's no longer a requirement for sequencing. That normally would trigger a revision and things like that, but it sounds like we don't have to do that.

The second component of that is, I'm interested-- we're interested in another clinical trial looking at T cell activation to assess individuals for their cellular immune response to vaccination or natural infection or to novel SARS-2 variants. And I'm wondering if the FDA is considering EUAs for those type of tests?

Timothy Stenzel: Would this be a serology test or a T cell functional test?

Don Cooper: These are cellular tests looking at blood draw using a T cell activation assay in response to a presentation of a new antigen.

Timothy Stenzel: Yeah, we're open to that. I made a promise to Francis Collins that we'd be open to that. Yeah, I mean, the T cell response appears to be very important. I don't think we understand very much right now.

We have authorized one T cell-focused assay. It was a sequencing-based receptor assay. That has been authorized and been used. And some important data may come out of that that informs us more and more about the T cell response.

But yeah, we're open to T cell functional assays. I would recommend that you come in with a pre-EUA for what you would like to do as soon as you're ready to do that to discuss your thoughts with us and have us to evaluate that.

It is-- typically, they're very low throughput, very manual assays, so there are clear challenges in developing and deploying such assays in any sort of volume capacity. Yet, they're novel enough and perhaps needed, as nothing else other than a tool to be used in clinical studies for treatments and vaccines. We do encourage, if you are interested in doing that, you do submit a pre-EUA and outline your thoughts.

Don Cooper: Do you think that the Breakthrough Designation or EUA-- would one go through both of those?

Timothy Stenzel: So a Breakthrough Designation is for a routine, full authorization submission. EUAs will not require as much information and data in order to get cleared. The Breakthrough Designation pathway is something that's available to all developers for submission. And the FDA will review those Breakthrough Designations and make a determination about whether or not designated as a breakthrough technology.

Don Cooper: OK, so to be clear, then, for the EUA submission on this, since it is novel, there is no template for T cell activation. This would be something that we would work together with after sending an email to the templates email site, and we'd have a back and forth?

Timothy Stenzel: What I would do is put this in what's called a pre-EUA. You can use, maybe, one of the serology templates and just fill in the information and make any edits to it about your assay. But we'd like to understand your assay design, your intended use, how you intend to validate it, and the intended use would include what sort of claims you would like around the results of such testing.

Don Cooper: Perfect.

Timothy Stenzel: So basically, we want to understand your technology, want to understand how you would validate it, and understand what you're looking for as far as an authorization.

Don Cooper: Perfect. OK, thank you.

CDR Kimberly Piermatteo: Thank you, Tim. We have time for one more quick question. Jacqueline, if you have a quick question, we can try to take that today.

Jacqueline, are you still there? I apologize.

Jacqueline Weir: Yes. I forgot to double hit on mute. Hi, can you hear me?

CDR Kimberly Piermatteo: Yes, we can.

Jacqueline Weir: Thank you so much. My group has a multiplex that we're hoping to get into clinical trials in November for. It's a flu, RSV, and COVID. We are anticipating to still have our low incidence of flu and RSV samples, so we're currently collecting RSV and flu samples to be banked for possible use during the clinical trial if we are allowed to do so.

Can you anticipate if we will be able to use frozen samples for RSV and flu if we're not able to collect prospectively? That's my first question. And then following that question is a concern that these are known positives that we would be using. So what kind of a study design is needed for when we're using previously collected samples that are known positives?

Timothy Stenzel: And can you tell me a little bit more? Is this a molecular test, or is it an origin test? Is it a point of care?

Jacqueline Weir: This is a point-of-care molecular test.

Timothy Stenzel: Point-of-care molecular test. So there's a lot more options, which I can't go into detail about why, for a point-of-care molecular test using banked samples. And there is some information, I believe, in the molecular point-of-care template about that. I do also recommend that you submit a pre-EUA for your study design.

We are going to want to understand how you sourced those samples, how they were selected from within whatever banks you got. We want to understand how you preserve those samples and if there's need for, say, a freeze/thaw study or a fresh/frozen study. Kris, anything else you would like to add about this question?

Kristian Roth: Yeah, I guess one detail is, does the user interpret the test results, or is it an instrument read?

Jacqueline Weir: It's an instrument read.

Kristian Roth: Yeah, so I mean, that opens up a couple of different possibilities as far as designing a clinical study when folks may know that they're positive. At least it hopefully removes some of that interpretation bias. But these are complicated studies, and flu is of low prevalence. And so I think we do have some recommendations for potential enrichment approaches that we could discuss with you in the context of a pre-EUA.

And I think, really, going to banked samples is a challenge. It depends on what kind of banked samples, you're --- what kind of sample you're banking. If you're banking a swab without transport media-- are you banking the swab in your proprietary transport media? So I think there's just some discussion about what that banking is. But I think we'd like to discuss, probably, enrichment prior to going to that banked sample.

Jacqueline Weir: OK, thank you.

CDR Kimberly Piermatteo: Thank you, Jacqueline. That was our last live question for today. Thank you to our panelists, Tim, and Toby, and Kris for their participation today. And we appreciate everyone else's participation.

As I mentioned earlier, a recording of today's Town Hall and a transcript will be made available on CDRH Learn within a week or two. You will find the recording and transcript under the section titled Specialty Technical Topics and then the subsection titled Coronavirus (COVID-19) Test Development, and

Validation Virtual Town Hall Series. Please visit CDRH Learn at the link provided on the slide to access those.

For additional questions about today's Town Hall and COVID-19 IVD topics in general, you may send an email to CDRH-EUA-Templates@fda.hhs.gov.

And lastly, please remember to join us for the next IVD Town Hall scheduled for Wednesday, July 27, 2022 from 12:05 to 1:00 PM Eastern Time.

Thank you all again for joining us. This concludes today's Town Hall, and have a nice day.

END