FDA Virtual Town Hall Series - Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests

Moderator: Irene Aihie
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Coordinator: Welcome and thank you for standing by. At this time all parties are in a listen-only mode until the question and answer segment of today's conference at which time you may press star 1 on your touch-tone phone to ask a question.

I would also like to inform all parties that today's conference is being recorded. If you do have any objections, please disconnect at this time.

I would now like to go ahead and turn today's call over to Ms. Irene Aihie. Ma'am, you may begin.

Irene Aihie: Thank you. Hello, I am Irene Aihie of CDRH's Office of Communication and Education. Welcome to the FDA's fifth in a series of virtual town hall meetings to help answer technical questions about the development and validation of tests for SARS-CoV-2 during the public health emergency. Today, Timothy Stenzel Director of the Office of In Vitro Diagnostics and Radiological Health in the Office of Product Evaluation and Quality and Sara

Brenner, Associate Director for Medical Affairs, and Chief Medical Officer for In Vitro Diagnostics in the Center for Devices and Radiological Health will provide a brief update.

Following opening remarks, we will open the lines for your questions related to today's discussion. Now, I give you Timothy.

Timothy Stenzel: Thank you and thank you to all who have joined us on this call today. Thank you so much for what you are doing every day to help in this pandemic situation. We are working hard and we are working together to solve the issues on a day-to-day basis and we welcome your collaboration and your participation in this process.

I'll make some brief introductory remarks -- mainly some updates. I'll turn it over to Sara for her to make some updates. And then we'll turn it over to question and answers. Look forward to that.

So again just briefly I have stated previously on some calls that the Abbott ID Now has now been updated to remove VTM as a sample type. I think we're trying to get the instructions for use update onto our website soon. Again, VTM as a sample type should no longer be used with the Abbott ID Now. Rather, the direct swab approach is one that should be followed.

Second, we've made a number of updates to our frequently asked question page. I would encourage you to review those on a regular basis and go if you haven't gone in the last week to go and take a good look at it. Some of the key updates that we made are that we have increased the number of the optional extraction chemistries, we've added the Kingfisher along with the RUO equivalent of the Kingfisher, the MagMAX. And those I believe are available through Thermofisher.

We continue to look at all available options. We are data-driven and data-based in these decisions and we'll update our FAQ page as soon as we can when we have additional options. We know that it can give you the at least spot shortages on swabs, media, and on extraction reagents. So we continue to work hard to provide the maximum flexibility from a regulatory perspective so that labs and developers can have options.

In regards to that, I did want to briefly remind everyone of some of the details of our March 16th updated guidance for labs who want to make certain modifications such as a change in swab media, extraction reagents, and PCR instruments. I simply do an (unintelligible) other bridging study that's appropriate under their own CLIA SOPs and compliant with CLIA. They can implement those changes without a EUA update. And we would love to see that on a voluntary basis so that we can perhaps make it more well-known. If you are adopting any swab, for a new manufacturer say, we would love to see that information but it's not required.

For IVD manufacturers, they can also make updates to their EUA authorization. Once they have submitted that validation to the FDA, they are immediately allowed to market that update under EUA while the FDA reviews that data and can make an assessment. We will obviously make a quick assessment of whether there are any risks and if there are, we would immediately reach out to the manufacturer. But we assume that those are validated properly. And as soon as we can review that package obviously we'll make an amendment authorization. And that's what we did yesterday for the Abbott ID Now example.

Let's see. One other major update is we did authorize the first home collection under this current emergency declaration. That was many of you may know it

was a home collection kit for the LabCorp (LDT). That is a narrow authorization only for LabCorp. They did extensive testing showing that this was going to be safe and accurate. We also because of the particular swap type they use - it's a Q-tip style cotton swab - that we asked them to do a fairly extensive quality control testing of each lot of kits.

So while the cotton Q-tip style swab is now authorized for one entity, we would urge anyone who wants to consider a Q-tip style cotton swab that they carefully look at whether that affects their testing performance at all. Does it impact the sensitivity near (LOD)? Does it impact the sensitivity? And that is perhaps not an ideal swap type to use but obviously we felt under the conditions of authorization for LabCorp that we're appropriately protecting patients and ensuring accurate testing.

So if any developers have any questions about that, we are happy to address that at CDRH-EUA-Teamplates@fda.hhs.gov. If you voluntarily want to show us any of your validation around these alternate cotton swab types, we would be happy to engage in a conversation with you. I would still remind all that home collection and/or home testing requires an FDA authorization before launching the EUA authorization. And this is to ensure that patients in the home, that safety is considered and that testing is accurate.

We are in conversations with a number of such developers. We see that this is a great advantage for a number of reasons. One of them is that patients perhaps can be assessed at a distance, thereby reducing the risk to health care providers who otherwise would be performing potentially invasive sampling specimen collection procedures that would potentially put them at risk of acquiring SARS-CoV-2. So there are a number of reasons in addition to that but that is one of the prime drivers here is to do our best to protect our health care workers who are out there every day being heroes. So thanks for that.

Let's see. Anything else in those general updates? We are continuing to take a look at saliva as a sample type. We believe that a preservative may be necessary that preserve the integrity of the RNA. It may destroy RNases. Some of the preservatives that are capable of doing that are potentially toxic, so that is an important consideration in addition to the accuracy. And we would ask that developers who are considering saliva as a sample type, that they come in and to discuss those opportunities with the FDA. And that we together can assess the accuracy and the safety of such a sample type.

Some of the data we have seen today has been variable and we have not been able to authorize based on existing data. And we are still trying to assess what the variables are around an adequate saliva sample that ensures accurate and safe testing.

Moving on, serology -- so to date we have authorized four serology tests. None of them yet are point of care even though some of them are designed to be performed in the near-patient point of care setting. And this is because data has not yet been submitted for anything that we could authorize yet that shows accurate testing in the lay user hands. That is usually the point of care patient setting.

These lay user studies are important as outside of trained laboratory professionals performing testing, we want to ensure that accurate test results are obtained.

I want to give an update on our interagency testing that's going on. It's a voluntary testing program. We have received the number of kits from a number of different manufacturers. Testing has begun. We will make results known as soon as we find a way to do that. I would just say that some of this

information is proprietary.

We are looking at ways to make that information known. We will in all likelihood offer those manufacturers who pass a certain bar of performance in this interagency testing a somewhat streamlined approach to EUA authorization. And that is one clear way that we can make the testing performance measured by this interagency team available to the public.

This interagency collaboration involves careful and great collaboration with entities such as the CDC, NCI, NIH, and (BARDA) and the FDA. So we thank our interagency partners for coming together in this awesome way to be able to assess the performance capabilities -- at least at certain levels -- on these voluntary manufacturers to come in.

We are also connected to other international efforts to assess performance across not just serology tests but other tests as well.

I would say that if we come into information that indicates that certain tests are not performing as expected and potentially are putting accurate results at risk or safety at risk, we will investigate all of those. And those include complaints. And we will address them accordingly to protect patients.

I would also say that we are nearly completed with a serology template that can be made public on our website. And look for those on our website to be made available as soon as we clear those with all appropriate parties internally.

Next, I would like to address a scientific issue related to serology testing. This may be known by most parties but I think it's important to review. When we talk about test performance at the FDA, we are not talking about the step by

step procedure that a laboratory person or a point of care person would do in order to obtain a result. When we talk about performance, we talk about what is the sensitivity of the assay, what is the specificity of the assay. And at times, depending on what the comparative is, we call sensitivity percent positive agreement and sometimes they call a specificity negative percent agreement.

Those are just an initial look at what performance is. It's also important -- and I believe especially for serology tests -- to understand what the prevalence of disease is as far as the impact on the actual clinical testing performance and what the clinical testing results mean. We look at things such as positive predictive value and negative predictive value to tell us in certain populations what is the impact of testing and in fact what is the impact of actual sensitivity and specificity.

When we measure sensitivity and specificity, we do require calculations of the 95% confidence interval. And we do look closely at the lower bound of the 95% confidence interval because for any given sample size involved in testing, the smaller the sample size the greater potentially the spread of the 95% confidence interval.

So for example, you may actually measure a fairly high specificity but if the sample size is low, the lower bound of the 95% confidence interval can be quite low. That is why we always favor larger studies over smaller studies. Some of the high volume, high-throughput serology central lab tests that we've seen the data on -- one of which we've already authorized -- tests more than a thousand patients for specificity determination. Obviously when you test that many patients, your 95% confidence interval is going to be even more narrow.

However, even though it's narrower, the lower end of the 95th percentile confidence interval is important for looking at the full range of possible results. And I would say that you know, some of the specificities are quite high, you know, in the mid-99 percentile-- so 99.5, 99.6 -- in the lower bound is around 99%.

If you look at positive predictive value in a population that has a prevalence of 1% we don't yet know what the actual prevalence of COVID-19 is across all of our communities in the United States and as an overall measure. Those efforts are underway and those efforts are very important for us to understand how to apply a given test sensitivity and specificity to your specific situation.

But I just wanted to give a couple of performance numbers so that you understand the impact of prevalence and specificity on actual positive predictive values. Positive predictive value is a measure of how many times out of a hundred is a positive result, a true positive. So if you take a test that is 99% specific -- and I'm using the lower end of the 95% confidence interval here -- and you measure it in a population that has a 1% prevalence of disease, your positive predictive value is 49%. That means only 49 times out of 100 is that positive result a true positive. The rest of the time it is a false-positive result. You might falsely assume a patient developed an immune response to SARS-CoV-2.

If you reduce the specificity of 95% -- that same prevalence of 1% -- the positive predictive value falls to 15.4%. Only 15 times out of 100 is that positive result a true positive.

One thing that we're examining is if you combine two serology tests back-to-back and you require a positive for both serology tests, how does that impact the positive predictive value. If you take two highly specific tests and that

same lower and bound of the confidence interval is 99% and you have the same 1% population, the positive predictive value rises to 98.9% -- a pretty decent number.

Even if you start out with the lower serology test that has a specificity of 95% but follow it up with a more specific test such as 99% specific in a 1% prevalent population, your positive predictive value rises to 94.5%. So just under 95% -- also a fairly decent number.

So I thought it was important to go over their performance characteristics of tests and how they're applied to populations and what a positive result can really mean and perhaps the importance of doing a confirmation serology test if the information from a serology test is important to you.

I want to just move on quickly to one other thing and that is they continue to hear complaints about inappropriate marketing or perhaps fraud. We do have a fraud email. We appreciate all submissions to that email.

And also I would also remind you that we have an active MedWatch going. You can go to the MedWatch FDA site and report any problems you see. We do review those complaints and those data and make appropriate decisions based on it.

With that Sara, I want to turn it over to you briefly before we go into questions and answers. Thank you.

Sara Brenner: Great. Thank you, Tim. I'll give a brief update on the topic of laboratory data harmonization. In this context, it's sometimes an overlooked but really essential aspect of understanding how many infections we have in the country at any given time. The detection of the emergence, prevalence, and spread of

infectious diseases is essential to inform efforts to protect and preserve public health from the local, state, and national levels.

So currently surveillance efforts are hindered due to inabilities to pool and compare data derived from laboratory diagnostics unless consistent reporting practices have been adopted electronically. At the core of this problem is a fundamental inconsistency and how tests are described where we're seeing with SARS-CoV-2 diagnostics, for example, the same test or a test meant to give the same type of answer is often described in different ways, which leads to ambiguities in the meaning of that information as well as an inability to roll it up or aggregate that data and understand it and analyze it collectively.

So as part of a public-private partnership, the FDA and APHL manufacturers, labs standards developers, CDC, and other agencies across HHS are working to ensure that molecular diagnostic testing for SARS-CoV-2 as well as serological testing can be described the same way from the get-go right out of the lab.

The terminology codes are currently being developed and assigned to each test to represent the question that the test asks of each specimen and the range of answers that can be generated from that test. This information will be extremely important in terms of addressing shortages for testing, ensuring that tests are working the way that they're intended to, and better understanding their performance in the field moving forward and expediting ways to validate and interpret how therapeutic or clinical interventions are actually working in terms of health outcomes as we move forward.

So simply by describing our diagnostic tests the same way from the get-go, the data generated from those tests can be used to gather more detailed information in real-time that will help us protect the nation and get back on

our feet.

We have email address that inquiries can be sent to. The email address that you can reach out to us at is SHIELD-LabCodes@fda.hhs.gov. That will be able to receive emails tomorrow, so hold off on emailing us until tomorrow if you're interested in this information and would like to participate in this effort. Thank you.

Timothy Stenzel: Thank you Sara. Operator, we're ready for some questions. Thank you.

Coordinator: Sounds good. If you would like to ask a question from the phone lines, please press star 1, unmute your line, and record your name when prompted. Your name is required to introduce your question. Again that is star 1 and record your name. If you need to withdraw your request it is star 2. Our first question comes from (Douglas Ross). Your line is open.

(Douglas Ross): Thank you and thank you Tim and Sara and everyone at the FDA for your hard work. Much appreciated. Well, I've got a question about whether a pathway will be created for home tests. I know that you are very interested in approving home tests as well as taking samples at home by individuals. But it appears that there is not a specific pathway for home tests -- just point of care.

Timothy Stenzel: That's a great question. We're striving to get the serology templates out as soon as possible. Maybe even today. That would be awesome. We are working on templates that could be used for home collection and home testing but they are not near ready yet to share.

In the interim, we asked developers to send us their inquiries at CDRH-EUA-templates@fda.hhs.gov. As appropriate we're happy to jump on a call and talk through the issues that we see and collaboratively work on a steady design to

show that testing is accurate. Hopefully, that addresses your question.

(Douglas Ross): Yes. Any estimate as to when they might be ready?

Timothy Stenzel: We've been actively discussing this and aligning internally for a while now as we engage with test developers in this area. Before we make something public, we want to make sure that we've properly vetted it so that it represents our best foot forward on just the right balance between ensuring accurate testing and safe testing and not being burdensome. So as soon as we can. It is a priority.

(Douglas Ross): Thank you, Tim.

Coordinator: Thank you. And our next question comes from (Brant Mittler). Your line is open, sir.

(Brant Mittler): Thank you, Dr. Stenzel. We previously in these webinars covered the issues of capillary blood versus venipuncture blood and the fact that the authorized serology tests have to be done in CLIA complex labs. Now, in light of the fact that Stanford has published studies -- at least in preprint form -- from Santa Clara County in which people drove, stuck their hand out the window, had finger sticks done, done on Chinese test kits. The same occurred in LA County. Hartford did a similar study using finger sticks a different kind of test kit in Chelsea, Massachusetts.

I'm wondering if you're still taking the position that there's no scientific evidence that capillary blood is equal to venipuncture blood in doing rapid test kits and doing the rapid test of serology. And also in light of the HHS guidance of April 8th, 2020 which just came to my attention in which it said that licensed pharmacists can order and administer COVID-19 test including

serology tests that the Food and Drug Administration has authorized, are you still taking the position also that licensed health professionals like physicians or nurse practitioners or PAs cannot administer the rapid test kits outside of a CLIA complex lab?

Timothy Stenzel: Yes, that's a great question. So we welcome all developers to come forward and show us their data for point-of-care testing. Fingerstick may not be required for point-of-care testing if there is the ability to do a venipuncture. We're open to fingerstick as a sample type. And our serology templates, once they're published, will describe publicly what we think the minimum number of patients are to demonstrate the equivalency, the matrix equivalency between venipuncture and fingerstick or serum and plasma and fingerstick. So that hopefully will be posted very soon for all to see.

So we are a data-driven organization that requires submission of data for us to review. We have given the opportunity for one authorized test to do fingerstick. They have actually agreed to do follow-on post-market study for the minimum number of fingersticks required for us to assess the performance there.

We also have invited them and others to do the usability study from the point-of-care to show that lay users, non-laboratorians, can perform accurate testing. So we do welcome submissions for those uses and are fully willing to authorize them.

Coordinator: Thank you. Our next question comes from (Julia Leslie). Your line is open.

(Julia Leslie): Hi, sorry. Can you hear me okay?

Timothy Stenzel: I can.

(Julia Leslie): Hi, Dr. Stenzel. Thank you so much for all the work you've been doing. I was looking into some of the serology tests and trying better to understand where there will be a future prioritization of more of these tests coming to market that can do point of care at high specificity and high sensitivity level in the coming weeks and this year looking at any right now.

Timothy Stenzel: So we are very interested in authorizing point-of-care tests -- both molecular and serology. As I said in response to the last question, we want to see the data that accurate testing can be performed in the point of care testing site in a wave setting with users that are not trained laboratory professionals. And if fingerstick is an important element of that point of care setting, to be able to see data show the equivalency for that particular test between point of care - I mean fingerstick and another sample type that's also been evaluated.

So we think this is possible. Our template will describe some minimum performance characteristics that we need to be able to see such as sensitivity and specificity. And an example is if specificity is not high enough, we would want to understand why that is. And perhaps more cross-reactivity testing with known potential cross-reacting respiratory pathogens may be required to understand the performance of that test.

As I said in my introductory remarks though, even if you have a very highly specific test - one of these very high-quality, high-throughput central lab tests which have studied over 1000 patients - the lower end of the confidence interval at 99% in certain populations may not be alone high enough to make important clinical decisions for that patient. And confirmatory serology testing may the important element serology testing -- making a decision based on even a high-performing test may not be sufficient to ensure that you know what really happened with that patient. Hopefully, that addresses your

question.

I would also add that performance at the point of care potentially could be a little bit lower as long as it's reflexed for confirmation to a higher-performing central lab test.

(Julia Leslie): Okay. Thank you so much.

Timothy Stenzel: Yes.

Coordinator: Thank you. Our next question comes from (Cynthia Flynn). Your line is open.

(Cynthia Flynn): Hello. Thank you again for these webinars. They have been great. My questions, what is regarding the Abbott ID Now issues with recalling the (VTM). I know I and a lot of other lab directors have a big issue about how we would then be able to verify the tests in our lab if we can only use a direct swap method. And I don't see anything in their package insert about how to do that.

Do you have any information about how to verify the direct swap method with the ID Now?

Timothy Stenzel: So for labs to do that, that is a little bit more challenging.

(Cynthia Flynn): It's required and...

((Crosstalk))

Timothy Stenzel: Yes. So you could contrive samples in the lab to verify testing. So take a known positive patient sample from VTM...

(Cynthia Flynn): Yes.

Timothy Stenzel: ...understand, you know, where the range of positivity is if you have a molecular test that gives you cycle thresholds. Find something near, you know, a low positive or dilute it down to a low positive. You can then pipe that on to swabs in replicates and test that in the Abbott ID Now. That would be one possible way to verify performance of the Abbott ID Now in your hands with...

(Cynthia Flynn): Right.

Timothy Stenzel: ...not having to go ahead and actually swab patients and swab enough patients that you get a positive patient to compare.

(Cynthia Flynn): Right and...

Timothy Stenzel: Hopefully that's helpful.

(Cynthia Flynn): Yes, and or do something like user (unintelligible) metrics for some other kind of control and he use that and diluted on to the swabs too. Yes.

Timothy Stenzel: Yes.

(Cynthia Flynn): Yes, I was thinking of that. And for the serology...

Timothy Stenzel: You would want to potentially dilute it into a negative...

(Cynthia Flynn): Right.

Timothy Stenzel: ...sample.

(Cynthia Flynn): Right.

Timothy Stenzel: ...so that you also test potential interfering substances that are present in the nasal swab.

(Cynthia Flynn): Right, correct. And then my other question is regarding the serology studies that you are doing, which are great that you're doing them. But are you going to be doing any (unintelligible) plaque studies during that time period so we start to know whether we're getting true neutralizing antibodies out of this type of testing?

Timothy Stenzel: Yes. I mean if you're really wanting to understand is the adaptive immune response producing antibodies that can fight the infection, you would want to know whether or not neutralizing antibodies are present. And for those clinicians who are looking at potentially using convalescent plasma to treat patients, you would also want to know are neutralizing antibodies present.

So we are an early dialogue with some developers of neutralizing antibody test. That is not something that's usually performed.

(Cynthia Flynn): Right.

Timothy Stenzel: And it would be, you know, and sort of uneasy to perform tests. So we hope to see more developers of assays that can measure neutralizing antibodies. And that would be very informative.

We do have the ability in some cases with some developers to try to correlate...

(Cynthia Flynn): Yes.

Timothy Stenzel: ... detection of antibodies and also in the same samples realize whether or not those samples have neutralizing antibodies. But unfortunately, it's not always clear that all the antibodies in the adaptive immune response are going to be neutralizing. So it's a bit of a challenge for the tests that aren't designed to measure specifically neutralizing antibodies to be able to make any sort of determination.

(Cynthia Flynn): Right.

Timothy Stenzel: So we believe it's important that it's clear that although some of these serology tests can accurately measure the presence of antibodies that arise to the infection, that it doesn't equate with immunity or the ability to fight off an infection.

(Cynthia Flynn): Right.

Timothy Stenzel: Hopefully that address is your question.

(Cynthia Flynn): Yes. Thank you very much. Bye.

Timothy Stenzel: You're welcome.

Coordinator: Thank you. Our next question comes from (Ariana Hawkins). Your line is open.

(Ariana Hawkins): Thank you. I appreciate you taking the call. My question is last week or the week before you had mentioned that you had assigned resources to develop a

template for rapid viral detection immunoassay. And I just wanted to check in and see you know, what the progress is on that.

Timothy Stenzel: Yes. We've made significant progress. And it's the priority as soon as we get the serology templates out is the next priority is the rapid antigen tests. And we invite all developers to come and dialogue with us. We obviously have authorized quite a few rapid antigen tests for other respiratory pathogens and so have a relatively good understanding.

We also know that the anterior nares may harbor enough virus to make these rapid antigen tests plausible. It would be ideal if they were on performance par with the new standards for say flu detection with rapid tests.

(Ariana Hawkins): Okay. Are there any concerns? I know probably we shouldn't ask about the other questions but are there any concerns about detection and comparison using the molecular test -- the PCR test -- for the comparator method as those will be obviously more sensitive than your average amino assay?

Timothy Stenzel: I think Labs who are interested in and other healthcare professionals that are interested in acquiring rapid SARS-CoV-2 rapid antigen tests are going to want to know what is the performance relative to molecular assays.

(Ariana Hawkins): Right.

Timothy Stenzel: So that is probably an excellent performance comparison to do.

(Ariana Hawkins): Okay. Right. Thank you.

Timothy Stenzel: Yes.

Coordinator: Thank you. Our next question comes from (Shannon Clark). Your line is open.

(Shannon Clark): Hello. This is (Shannon Clark) with User Wise. We specialize in home use usability testing for diagnostic products. I was just listening to the call and wondering would it be helpful if we prepared a template for you for home use serology testing?

Timothy Stenzel: We would love assistance. We can't promise that we'll incorporate the idea but you certainly can send your ideas into our CDRH-EUA-templates@fda.hhs.gov email address and we will take a look at it.

(Shannon Clark): Okay. We'll send it in. We've been working with the human factors team at the (unintelligible) repair protocol for another research project that we're working with FDA on. So we'll leverage that and will send something over by the end of today. But that actually wasn't my question.

My question is pixel for the home usability testing -- which I would assume was performed -- can you share whether you required 15 laypeople and whether it was a clinical home usability study with clinical endpoints rather than just a pure usability study with no clinical endpoint?

Timothy Stenzel: So it was a simulated home use testing sort of environment with folks inexperienced with collecting a nasal swab on themselves given only the directions in the kit to perform. And we were able to assess adequate sampling in these situations important features of an assay that utilize such home or self-collection is that there are internal controls that are able to assess whether the sample is adequate they obtained.

(Shannon Clark): Definitely. Thank you so much. And again this is (Shannon Clark) with User

Wise. So you'll be hearing for my team later today with the template for a serological validation for home use.

Timothy Stenzel: Thank you, (Shannon).

Coordinator: Thank you. My next question comes from Miss (Carney). Your line is open.

(Carney): Hi. So I have two questions. One was for the cross-reactivity. We're making a test for IgM IgG antibodies and we have a panel of seven that is recommended but we couldn't find all seven. We got five. Is that okay? And the second question is for class specificity. Can you explain more on how we can demonstrate that our test can detect IgG and IgM both?

Timothy Stenzel: So our template -- which hopefully will come out very soon -- explain the number of these situations. In the interim, you can engage with our expert FDA staff through the template email.

But in general, there are alternate ways to achieve adequate assessment of cross-reactivity. For example, obviously the more known samples with known convalescent plasma or serum that you have that's specific to certain respiratory viruses is helpful in our assessment. However, you can test a minimum number of negatives -- a variety of negatives -- some of which, many of which can be pre-COVID-19 but not too old. We want to see folks that have been exposed recently to a variety of respiratory pathogens.

And so by simply assessing you know, enough negative patients you can get a surrogate assessment of potential cross-reactivity -- especially as it relates to the general population. So that is an alternate way to do that.

And the template will layout minimum numbers which I don't want to speak

to right now because they haven't been totally cleared for representing that publicly. But we will post it on our website as soon as it is cleared. And in the interim, you can get those numbers from our staff. So there are two alternate ways of going at that.

And as far as class specificity goes, our template will also outline multiple methods to achieve it. One is you may have well-characterized anti-IgG, anti-IgM antibodies for the detection. And so if those antibodies are well characterized for other potential uses that you have used them for, those previous studies can be used does evidence. There are also chemical ways of achieving this is well and those will be outlined in the template that are you now waiting for final clearance.

(Carney): Okay. And just real quick so then we did a validation but to notify it can we if it's not correct can we still use the template or how would that work?

Timothy Stenzel: So through pathway C or D, developers can let us know that they have completed validation and launch. If you're interested in an EUAauthorization we when we receive the EUA package we will take a look at the acceptability of the studies and the study designs that you performed. If there are no outward signs of risk to inaccurate results, we will work with you and allow developers to stay in the market while we assess potential additional studies.

So that's our general way of handling things for years and years here in similar situations.

(Carney): Okay. Thank you.

Timothy Stenzel: All right. Yes.

Coordinator: Thank you. And again as a reminder please limit yourself to one question. And our next question does come from (Michael Ross). Again, one question.

(Michael Ross): Yes.

Coordinator: Your line is open, (Michael Ross).

(Michael Ross): Thank you very much. Much appreciated, the prevalence discussion versus specificity. We just had that in our group. I had a very simple question which has been talked about before but still is unclear. As I recall from the last session if you have your EUA you could or would be cleared for non-CLIA laboratories to use. However since the FDA doesn't control CLIA, how does that work? What is the mechanism?

Timothy Stenzel: Yes. So first of all, those developers that notify us through pathway C or D are automatically put into a high complexity category. And that should be those that we have listed already, those should be designated on our FAQ page now in such a manner as H for high complexity. As soon as we're able to authorize them and if we authorize them for moderate complexity situations and/or waved situations, the website authorization will be updated with that information and the website will be updated as well.

So we take a traditional approach on assessing whether a technology is acceptable for other than a high-complexity environment -- whether it can be moderately complex or a wave setting. We do not do a formal complexity determination as we could do outside of an emergency situation. Our office at the FDA is legally responsible for making those assessments for CLIA categorization. That task has been assigned to our office and we have staff who are experienced in that.

In the emergency use situation, we are allowed under law to deem a test as moderately complex and/or waved. It is not a formal classification. We make that deemed status clear in our authorization letter and in a language that's allowed in the developer's instructions for use. And we'll make that publicly available clearly on our website as well.

(Michael Ross): That's great because we did have some issues with what are the major local hospital groups who thought that was a very confusing point. But I appreciate the clarity now.

Timothy Stenzel: Yes. You're welcome. Thank you.

Coordinator: Thank you. Our next question comes from (Karen Richards). Your line is open.

(Karen Richards): Hi. This is (Karen). Can you hear me?

Timothy Stenzel: I can.

(Karen Richards): Okay. So if you're a high-complexity lab using an FDA approved EUA molecular test that's authorized for respiratory specimens, does FDA require a EUA submission if that lab wants to validate and use saliva as a sample type? Or can they perform that validation under their CLIA license?

Timothy Stenzel: Yes. So that frequently involves a collection device that is not formally covered under you know, the COVID-19 diagnostic situation. We have also seen data from saliva that is not really good enough for clinical use. So we are currently asking developers who want to utilize saliva -- and we do encourage it because we obviously already authorized one such test -- to come in and discuss their design with us and make sure that whatever data is generated it's

going to be sufficient for us to say yes, that looks good.

And, you know, until such a time that we can define the true performance of saliva and we can predict the performance, we think this is the safest way to go right now. And there is - some of the data is just not good enough to support it and we don't know all the variables such as how do you need to preserve it, how do you store it, how do you transport it, and how do you extract it. And then what particular tests perform well on saliva-based samples.

(Karen Richards): Thank you.

Timothy Stenzel: You're welcome.

Coordinator: Thank you. Our last question comes from (Daniel Schultz). Your line is open.

(Daniel Schultz): Thank you very much. I just want to thank you all very much for being so open and transparent. I'm the Medical Director VP of Medical Affairs with LifeNet Health and I'm an Autopsy Pathologist. The question I have is how do we gauge the performance -- namely the true positive rate in the population without - what measures are we using to do that? We're not seeing autopsies in general. We're generally not seeing tissue sampling. What are the methods being used to gauge that true positive rate?

Timothy Stenzel: Yes. Extensive molecular tests could help but that only tells you a snapshot of time for when patients are shedding detectable virus and the assay performs well enough. Serological means are probably the better means of assessing what the true prevalence is in a given population.

Some of the studies I've seen may be limited to the performance of just one

maybe point-of-care test for which the true performance characteristics, the true specificity may not be entirely known. And so when you do an assessment you may say we just did a hundred samples. They were all negative. Therefore, our specificity is 100%. But that may or may not be the case.

Using statistics, the application of a 95% confidence interval to the data set is important. And so the more day that you have, the more assurance you know what the performance is. I would postulate though that the best way to assess prevalence through serological testing means is to take two very high-performing but different tests that utilize different antigens -- not the same antigen -- to detect these antibodies.

You may limit yourself to IgG, which is probably the most important antibody. IgM presents some difficulties maybe even in specificity sometimes. So if you look at two high-performing IgG tests -- and it might be just the IgG component of a combined test -- and if they are both positive, your ° of certainty around whether the assessment of prevalence in the population is going to be much greater.

If you choose to test that have relatively high sensitivity, you're not going to lose a lot of sensitivity in requiring the due positive. For example, even if the sensitivity for the two tests is only 90% your overall sensitivity for requiring the combined positive results only falls to about 81%. So obviously the higher the sensitivity for each of those two serological tests, the lower your sensitivity falls.

But knowing you know, the true performance on a lot of samples for these serological tests will give you a better estimate of what the range of performance characteristics are and you can take that into account. But again I

think to be conservative you ought to take the lower bound of the 95% confidence level and not go any higher than that for both sensitivity and specificity calculations. Hopefully that helps.

(Daniel Schultz): Yes. Thank you very much. Sometimes it seems like there's a bit of magic with the prevalence and at the true positivity. There are definitely estimates. Thanks.

Timothy Stenzel: Yes. You're welcome.

Coordinator: Thank you. And I would now like to go and hand today's call back over to Ms. Irene Aihie.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on the CDRH Learn web page at www.fda.gov/training/cdrhlearn by Monday, April 27th. If you have additional questions about today's presentation, please use the email address CDRH-EUA-Templates@fda.hhs.gov.

As always, we appreciate your feedback. Following the conclusion of today's presentation please complete a short 13 question survey about your FDA CDRH virtual town hall experience. The survey can be found at www.fda.gov/cdrhwebinar immediately following the conclusion of today's live session.

Again, thank you for participating and this concludes today's discussion.

Coordinator: Thank you for your participation in today's conference. You may now disconnect at this time. Have a wonderful day. Speakers, one moment.

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