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

**Moderator: Irene Aihie
October 21, 2020
12:15 pm ET**

Coordinator: Good afternoon and thank you all for standing by. For the duration of today's conference all participants' lines are on a listen-only mode until the question-and-answer session. At that time, if you would like to ask a question press star 1. Today's call is being recorded. If you have any objections you may disconnect at this time. It is my pleasure to introduce Ms. Irene Aihie. Thank you ma'am, you may begin.

Irene Aihie: Thank you. Hello. I'm Irene Aihie of CDRH's Office of Communication and Education. Welcome to the FDA's 31st 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 Toby Lowe, Associate Director of the Office of In Vitro Diagnostics and Radiological Health, both from CDRH, will provide a brief update.

Following opening remarks, we will open the lines for your questions related to today's discussion. Please remember that we are not able to respond to questions about specific submissions that might be under review. Now I give you Timothy.

Dr. Timothy Stenzel: Welcome everyone. A pleasure to be on the call again with all of you. So I appreciate all of your creative minds and dedication to addressing unmet COVID pandemic needs. We look forward to working with you.

You may start to realize that you have additional folks who you've not met before. We've been hiring and we've been shifting some resources to try to work through all of the volumes of submissions as quickly as possible. We've been doing that since day one and we continue to do that. So hopefully that has a net positive influence on all of us.

Just to start off, I wanted to talk about something that's very important to all of us as test developers and those involved with validation and authorization and use of these tests in this pandemic. It also applies to non-pandemic situations. I do want to help enlist your support and help in educating all of the various stakeholders who utilize these tests in different situations.

So I wanted to talk about false positives again. We continue to hear about challenges relating to getting false positive results. And I would add, even in situations where it's totally expected that might seem odd. So first of all, there is no - I'm not aware of any perfect test. And I want to go back to my example of using a test, whether it be an antigen test or a molecular test.

Neither - I don't know a single one that's perfect, that is 100% specific that is every time a patient is truly negative the test is negative. It just doesn't exist to my knowledge. So if we just assume for a second just for the math, that 99

- the specificity of any of these tests is 99%. It is 99 times out of 100 a patient who is negative will test negative. And only one time out of a 100 will a patient who is negative test positive.

I think that's a very high specificity for almost any category of test. The challenge of course is if we begin to test in large scale screening, whether it's antigen or molecular, and we're screening populations that in particular, have a low percent positive rate, if that percent positive rate falls below the 1% false positive rate, it means that even for a perfectly well-functioning test it's a well-designed test, it's a well-validated test and the users who are performing the test are following the instruction, this, you know, according to the package insert, they are going to get a 1% false positive rate if the test is 99% specific.

And it really doesn't matter if the patient is symptomatic or not. If the asymptomatic it applies the same. And it doesn't even really matter if a test has achieved a claim for screening asymptomatics. Specificity - is specificity typically going to be the same in all of these different populations for a given test format, a given sample type?

And so the challenge is what do you do when the false positives which are totally expected, outnumber the true positives? I think it's important to say this is a totally expected situation and we plan for it. And we plan for it by - in those situations where the prevalence of positive disease, where the percent positive is low, significantly less or even in a, you know, even if it's a 1% positive rate you're going to have - half your positives are going to be false positives and half your positives are going to be true positives.

So unless your percent positive rate is pretty high the idea that you might have as false positive is going to - if it's going to impact somebody's livelihood that is they may be asked to quarantine themselves for 14 plus days, or it involves

putting a patient into a risky situation or healthcare workers aren't alerted to a patient having this or it determines outcome. You know, if they have flu they're going to treat somebody this way; if they have SARS they're going to treat them another. So all those situations matter.

And you know your population is such that the false positive rate is not insignificant. And it's important and I would recommend that you get some sort of orthogonal confirmatory test done. I would prefer it be a molecular test of high specificity and sensitivity. You know, there is the option potentially of using another direct antigen test if your primary test is a direct antigen test.

What I don't think we have a good handle on yet is whatever causes a false positive for one test, in particular a test that doesn't have an extraction of nucleic acid step up front, you know, if there's something in that sample that lends itself to a false positive result in a given individual, if you just fully go to another different orthogonal or direct antigen test, I just don't know at the moment and maybe somebody does, if you do please reach out to us through our Templates email address, you know, if that second direct antigen test will give you a true result based on the sample having certain potential characteristics that may lend itself in a direct antigen test to giving you a false positive. So I don't know. I think - I personally lack the information to give a recommendation on that. I would be very interested in seeing data about two orthogonal direct antigen tests and when you have a false positive, you know, can you use that orthogonal test to determine that?

The other thing is if there is any sort of loss of sensitivity with a direct antigen second test, a high sensitive - a highly, highly specific molecular test is more likely to give you an accurate confirmation of whether you have disease or not.

So that's the introductory remarks for today. Thanks again for joining us. And I look forward to your questions. Thank you so much.

Irene Aihie: Operator, we'll now take questions.

Coordinator: Thank you. If you would like to ask a question please make sure your phone is not muted, please press 1, star 1 and when prompted, clearly record your first and last name so I may introduce you. Again, to ask a question press star 1. Our first question is from (Alberto Gambini). Sir, you may go ahead.

(Alberto Gambini): Hello. Hi. Can you hear me?

Dr. Timothy Stenzel: Yes.

(Alberto Gambini): Yes. So my question is related to the - once the staff, the NIH staff ensure the FDA - to ensure that the validation done by the NIH is done according to the instructions of the packages of the test being tested. We know in at least one case the NIH has not followed instruction as far as for example, using sample matrices not intended to be used in this assay for example, using different test plasma coagulated with a different anti-coagulant than the one the sponsor actually providing and validated.

It seems to be to me a pretty curious evaluation of the instruction of use. And also to now follow in some cases, at least one case, you know, do not use the proper specific controls to ensure that the operator knows how to use the test. Some of these tests may be new technology and so the operator would have to sort of train on it.

And I'm wondering this can have a serious impact because you conducted basically, you know, validating incorrectly either in a good way, a bad way or whatever you like to see it as an assay. So I would like to know what kind of steps you may take and if there's any concern about the NIH's mishandling of the assay during the validation.

Is there any possible way for the sponsors to discuss that either with the NIH or with the FDA or all three together? Thank you.

Dr. Timothy Stenzel: Yes. Well first of all, the NCI is doing a fantastic job and such an important job. And we have processes and procedures in place to try to ensure that in all cases package inserts are followed and that the correct sample types are used.

We don't have the luxury of getting a wide variety of panels for each different kind of sample type as far as serum or plasma and then as far as the plasma for the anticoagulant that's used. And so we are somewhat beholden to the panel as it gets formulated and therefore, we do want to look to those situations where, you know, a non-ideal sample type was used.

We typically can look to (ADAS), look at as subset of the result that match and line up with the IFU for the product. If that is missed we - when we get the results we do reach out to sponsors with their NCI results. And that is an opportunity for sponsors to engage in a conversation with the FDA to address those specific questions. And a few times it has come to my attention of this and we've done our best to address those concerns.

So that's an opportunity for sponsors when we give you that feedback, on the results. The panel does use serum and plasma and it does -for plasma it does use, you know, the common anticoagulants, you know, in general. So, you

know, and there may be some tests that have limitations on serum versus plasma and vice versa and for plasma, the type of anticoagulation.

So we appreciate working with sponsors to help us if we overlook something either at the NCI or at the FDA. And we'll do our best to properly address that situation. So if you feel that's not the case you can always reach out to Toby and me through the Templates email address for a specific discussion and a specific situation.

(Alberto Gambini): Thank you.

Coordinator: And our next question is from (Louis Perlmutter). Sir, you may go ahead.

(Louis Perlmutter): Yes. Thank you, Tim and Toby. The question really concerns whether there are any approvals for the recent - for recently submitted rapid antigen immunoassay tests for the SARS-CoV-2.

I'm not thinking of the BinaxNOW test by Abbott, but any others. Are there any in the works?

Dr. Timothy Stenzel: So we have posted all of those that we've authorized. The IVD EUA authorized at the FDA. I believe there are six and I believe Quidel came in subsequent to the BinaxNOW test with a Flu A+B SARS test. So you can always see what's within, you know, we post that within, you know, an hour to 24 hours or, you know, and business days after authorization. If it happens over the weekend then it usually happens on - it may happen not until on Monday.

And there are a number of developers working on additional rapid antigen tests. And I can't go into any more specifics than that, but…

(Louis Perlmutter): Yes. Okay. I was aware of those. There are a few submissions. Yes. Okay. Thanks very much.

Coordinator: And our next question is from Alexis Sauer-Budge. You may go ahead.

Alexis Sauer-Budge: Hi. This is Alexis Sauer-Budge from Exponent. I was hoping that you could give us a little bit more detail with regard to the announcement about the FDA declining to review LDTs. You've also stated that it's a high priority to review high throughput tests. So if a CLIA certified lab is developing an ultra-high throughput molecular test would you still review the submission?

Dr. Timothy Stenzel: So we are currently declining to review LDTs and for the reasons that we stated on our FAQ page. And that is largely because they - the FDA cannot require an EUA and - according to the HHS statement. As far as high throughput goes those are for those tests that then we choose to review due to the, you know, unprecedented number of applications.

We want to focus our resources on those that do require an EUA. And so a single lab that's developed their own test and it happens to be high throughput, you know, doesn't - if that's, you know, sort of the specifications of that its' our understanding it doesn't require an EUA. And so we are focusing on high throughput situations now.

Some of that's, you know, going to be, you know, kits that have incredible amounts of automation where you load samples and step away and they have a high throughput. So we talk about high throughput, you know, being a high priority. It's that sort of situation where in particular, distributed kits.

So if, you know, the kit is high throughput, the instrument is high throughput and it's able to be offered in a lot of different labs, that's going to have a huge positive public health benefit and that's where our attention is going to be focused among the other high priority items and those items that do require an EUA prior to launch.

Toby, do you have any other comments?

Toby Lowe: No. I think exactly what you said. We're focused on distributed tests and that includes high throughput distributed…

Alexis Sauer-Budge: So…

Toby Lowe:

Alexis Sauer-Budge: Thank you for that. If I could just have a follow up then. If the intent though was to provide the protocols to other laboratories a - so, you know, buy these particular pieces of equipment and use this protocol sort of similar to the Yale SalivaDirect protocol, is that an avenue that would make it not an LDT and the FDA would review it?

Toby Lowe: So without all of the information for a specific scenario it's difficult to give an absolute answer. But I can tell you that the SalivaDirect test that you're referring to is considered to be a distributed test.

Dr. Timothy Stenzel: And not an LDT.

Alexis Sauer-Budge: Great.

Dr. Timothy Stenzel: In fact I don't believe that Yale actually has a lab that - the developers don't have a lab that they're doing clinical testing in. So they are basically a kit that has the instructions and then everything needed for the kit is required but not provided and that's the way we view that.

Alexis Sauer-Budge: Great. Thank you so much. And thank you for all the hard work that you're doing to help us with this pandemic.

Dr. Timothy Stenzel: You're most welcome.

Toby Lowe: Thank you.

Dr. Timothy Stenzel: Thanks for those kind words.

Coordinator: And our next question is from (Christopher Benson). Sir, you may go ahead.

(Christopher Benson): Hi Tim. I'm calling again to update you since we last spoke about this, about two weeks ago, about shipping the SARS-CoV-2 FDA panel overseas. We've made substantial progress. I work with Dr. (Mayra Garcia) at your office. But we did receive a request from the foreign country for a certificate of inactivation from FDA for the panel. I thought this was a reasonable request. Do you know if you have that kind of certificate?

Dr. Timothy Stenzel: Toby may know. You know, this - we have processes and procedures within the FDA. We received live virus, we grew it up with - on the FDA campus in a BSL-3 facility. We followed a protocol, an institutional protocol that was reviewed by the FDA to make sure that it was safe for our employees and I think we did the same for the inactivation.

What I don't know is - and so we have complete confidence that it is safe to distribute as a BSL-2 level panel. But what I don't know is if we have the ability to provide such a certificate. And there may be an opportunity to write a letter rather than say provide a certificate.

So - and I'm not sure if you've had that conversation with (Mayra). It's not coming to mind. I meet with (Mayra) a couple of times a week if not more frequently. Toby, do you know anything more and…

Toby Lowe: I don't know whether or not we have that certificate. But we can - (Mayra) would definitely know. She's just not online at the moment because she's in the lab I believe. But we can definitely find that out.

(Christopher Benson): All right, thank you. Yes. I wrote to (Mayra) and…

Toby Lowe: Okay.

(Christopher Benson): …most of that's - so maybe a letter would be sufficient. The other thing they recommended is a limit of 10 kilos for the dry ice shipment which I'm sure is due to international flights. But I'll follow up with (Mayra) on that. Thank you Tim and Toby.

Dr. Timothy Stenzel: Well that's a, you know, that's not a lot of dry ice especially if you're shipping international, which I - fortunately or unfortunately substantial amounts of experience with, having been a Chief Operating Officer who has shipped internationally in my previous role.

So the other thing is that we have worked with some sponsors who have found a facility or lab that can work with - in the US, to do the testings for them. And, you know, where there were challenges in shipping internationally. So

that is a potential avenue as well. It's not, you know, required or even recommended. It's just a statement of fact.

(Christopher Benson): Okay. I appreciate that.

Dr. Timothy Stenzel: Thank you.

(Christopher Benson): Thank you.

Coordinator: And our next question is from (Elliott Millinton). You may go ahead, sir.

(Elliott Millinton): I had a couple of questions. One is, is there a panel for an antigen test validation for a rapid antigen test?

Dr. Timothy Stenzel: Not yet to my knowledge. And there have been fairly detailed discussions about what we can do in this area. One of the concerns relates to the prior conversation about the fact that this is a BSL-3 level virus and we - most folks don't have a BSL. Most developers in labs don't have a BSL-3 facility so that they can safely handle it. There are some, but most don't.

And therefore, I'm just going to tell you that transparent issues that we're facing. So you can go ahead and inactivate that virus in a number of different ways. And then you want to make sure it actually still functions at the antigen level. And it's going to be challenging to, you know, provide that kind of assurance that it's going to behave just like Wild-Type, live virus.

But we are looking into it or, you know, our methods of inactivation to make it safe. We are looking into how well it performs. We're also looking at potentially the opportunity to express antigen and make protein. And then

obviously you get away from the need for inactivation because it's not whole virus and should be very nontoxic.

So we're working on it and I'll say that we're working on it within the US government and there may be others outside the government who are working on it. We're just not ready to move forward but we certainly are very interested. So thank you for your question.

(Elliott Millinton): Thank you. And when you say you'd have to make sure the antigen still functions, first of all, do you have any preference for heat inactivated versus radiation inactivated? And how would you recommend determining whether it's still functioning?

Dr. Timothy Stenzel: Yes. So I don't know that I have a preference there as far as I think, you know, the way to go about this is to try a potentially different method and conditions and see if it - see how robust that is. And then see how it impacts, you know, at least the EUA authorized antigen test.

But again, they're not cookie cutter. The direct antigen tests are not cookie cutter. And if they are using antibodies that are different those antibodies then in most cases, are going to see a different epitope. And that could be very - different epitopes can be variably impacted by different methods of inactivation.

Likewise if you began expecting proteins, if it doesn't - if the proteins aren't processed and get the non-nucleic acid directed modifications in the same way as in human cells then there could be alterations in performance.

So they're just very clearly additional challenge when you try to develop a direct antigen reference panel as compared to a reference panel for molecular

that we can basically inactivate, know that we inactivate, and know that if the RNA is there and stable that we'll have uniform good results.

(Elliott Millinton): Thank you. And one more question - for a - for validating an antigen test with saliva, can it be compared to a PCR test with saliva and do you have a preference as to whether it's a saliva sample for PCR or a nasal swab sample?

Dr. Timothy Stenzel: I think that's a great question. I think it's important to - whenever you're doing kind of comparative tests, so just to make sure with the FDA staff in our office that it's an okay comparator. I would say that if it's an EUA authorized high sensitivity molecular method there's good chances that you could use saliva as the comparator, molecular saliva for the antigen comparison. But I would say it can depend and just double check with our team.

Toby Lowe: I don't have it up in front of me right now, but I believe the antigen template discusses appropriate comparators and specifically mentions no saliva. So if you are particularly interested in using saliva as a comparator I would recommend reaching out to the antigen team prior to beginning that study, to discuss that.

(Elliott Millinton): Great. Thank you.

Dr. Timothy Stenzel: And that would be to an alteration to what's recommended. And, you know, over time our thinking can change and we try to remain open. Now that we have a lot more saliva experience the team's thoughts may have changed. I'm not going to speak for them though.

(Elliott Millinton): Thank you very much.

Coordinator: Our next question is from Edward Strong. Go ahead sir. You may go ahead.

Edward Strong: Hi there. Thank you. Yes. Edward Strong from iAssay in San Diego. So we have a handheld portable reader instrument that reads lateral flow devices and other formats of rapid tests. You know, iAssay's model is we make that instrument and then we work with part and developers of other testing devices.

I think you probably remember, on last week's call you indicated that there may soon be some guidance on instruments, especially now that there's recognition that instruments like the reader, would be beneficial to improving or preserving the sensitivity and reporting in offsite testing. I was just wondering if there was any update that you might have to provide on that guidance on that front?

Dr. Timothy Stenzel: Yes. So Toby wasn't here last week. I terribly missed her. And she may know the latest. It was my desire to have some additional recommendations - oh, two weeks ago Toby was here - wasn't here. And I believe that we may - we made some adjustments to the appropriate templates but those have not been posted yet. And I don't think we can say when it can be posted.

But I do believe that guidance can be given and this would - if I remember correctly, this was for a serology test. But potentially the same could be applied to direct antigen test. But I think it was around, and my input was around what to do for serology tests.

So I believe an email to the FDA staff can provide some recommendations based on our current thinking until that guidance is posted. And we're obviously - Toby, do you have anything else to add?

Toby Lowe: Yes. I think we've had some emails with you as well on this topic. I think that, you know, the main point is going to be that we need to see evidence that the reader works with a specific test. And so that's what we're going to be most interested in. We do have some experience with readers outside of the public health emergency where the readers have had a - potentially can have a negative impact on a test performance.

So we do want to see those paired together. And there, you know, we would be happy to work with you on the best pathway to do that, whether it's working directly with the EUA holder for the test, where they could come in with an amendment to, or a supplement rather, to their EUA.

We can, you know, we're still having some discussions internally about different options there. But that's something that we can work with you on. But the biggest point is that we really do need to see the data with the test and the reader paired together.

Edward Strong: Okay. Yes. If I could ask a follow up question. That's particularly…

Dr. Timothy Stenzel: Yes, go ahead.

Edward Strong: …the area that we were thinking about, you know, obviously working with some developers with their EUA submission. But yes, we were looking at iAssay for guidance on if we could supply data that we preserve the performance of these tests but do it independently of the developers because their model's very much like an independent open platform for our reader to be functional in many different serology or antigen tests.

So it sounds like you're having those discussions internally. And maybe we'll reach out again and get some guidance on that direction.

Dr. Timothy Stenzel: Yes. And so Toby was talking about accuracy determination. And I'm - I was talking more - that's important as well. But I was thinking a lot more towards the flexibility and regulatory pathways for some, for reader developers and, you know, what might be required of the reader developer that could be independent - or recommended reader developers that could be independent from the lateral flow test itself.

In the end, you know, just to be transparent and clear, it would - and unless you were to repeat all of the validation studies that the original manufacturer did for their EUA authorization, get your own EUA authorization, you're going to want to rely on the data that's already been accumulated and EUA authorization, if it's authorized, for that test.

And that will require some sort of letter from the test developer to the FDA saying that they give permission for a particular instrument developer or reader developer, to use that data in their submission to have a reader that can specify that it works with that particular lateral flow.

So that was a lot of words, but basically in the end, even if you do things independently and I suggested edits, that would allow some independent so that it makes it as easy as possible to add readers, it still requires a collaboration on some level with the company that developed the lateral flow device.

Edward Strong: Of course. This is perfect. Very helpful. And I echo what everybody else has said. Thank you, guys for the sleepless nights and you all deserve a vacation. Thank you.

Dr. Timothy Stenzel: Thanks so much.

Toby Lowe: Thanks.

Coordinator: And our next question is from (Kotamudi Venkep). Go ahead, sir. Your line is open.

(Kotamudi Venkep): Hi. Good afternoon. Can you hear me?

Dr. Timothy Stenzel: Yes.

(Kotamudi Venkep): Yes. Thank you for taking the question and thank you for all the updates. My question is related to the initial remarks that you mentioned about the false positives. If you are giving an example of 99% specificity, one out of ten is a false positive. And at the end, you know you were mentioning about the - if an antigen test is there you can do orthogonal test with the secondary test.

Is it only for the antigen test or even for molecular test? So any positive test if there is a - it can be potentially false positive that needed to be confirmed with another test? I did not get what you were mentioning clearly. Can you please elaborate and clarify that now please?

Dr. Timothy Stenzel: Yes. Yes, no, it - this also applies to molecular tests. They're not perfect either. Developers do their best, you know, and users of those tests do their best. And, you know, in my conversations with those who are doing pure surveillance which for this pandemic, is not something under the purview of the FDA but yet we still have a lot of conversations, this is typically done on a lot of different educational campuses around the US. They oftentimes use molecular means.

And in the ones that I've spoken to specifically about this, they do have false positives and they do - first of all, if they have a positive, you know, they want to move it into the CLIA lab to be able to - in some situations at least, to provide a CLIA result rather than an unregulated surveillance result which, you know, is cautioned against obviously.

But they have found that they do want to do their confirmatory testing. So and particularly as I said, in a low percent positive population, you know, and I've talked to some who have rates of detection of positives that are well below .1%.

So when you start to get into a positivity rate, you know, well below not even 1%, below .1%, you are absolutely going to get into territory with even extremely high specificity tests you're going to have some false positives. So you do want to do some sort of confirmation. Hopefully that's helpful.

(Kotamudi Venkep): So it is only, you know, when if it is a - you are 99% specificity. So only if you are testing a population where it is less than 1% then this approach is useful. It is not for other diagnostic tests even if it is…

Dr. Timothy Stenzel: I think it's something to - that every clinician or healthcare worker that interprets positive and negative results of testing, no matter what kind of testing it is, needs to keep in mind. It's a very important thing to keep in mind. The - it's one result and it could be a false positive, it could be a false negative.

What we do at the FDA is make sure that these tests perform at a certain level and we make public that performance information so that the users of these tests whether it be labs or it be clinicians, can make an informed decision

about what does a positive result mean in this patient, in the population that I'm testing?

You know, is the patient symptomatic or are they asymptomatic? You know, have they been exposed or not exposed? So this is a very complex science to properly interpret the results of tests. What I was really urging folks to do is not to assume in low incident populations, that a positive is a true positive, just is a chance of false positives.

So as your percent positive rate increases, say it increases - I mean there are some states I'm saying wow, they're over 30%. All right. Let's just say 20%. Let's say percent positive in the population is 20% and your false positive rate is 1%. It means that you're going to have 21% positive rate, 1% of that is a false positive, the rest of it is true positive.

So it means that - or it was just say overall, the measured rate is 20 to make the math easier. So that, you know, 19% true positive rate, 1% false positive rate, your percent positive overall including the false positives is 20%. One out of 20 is a false positive or 5% is a false positive.

But you just, you know, if you're a clinician interpreting results or you're a laboratory interpreting results, you just want to know that. What are the chances that this individual result based on the performance of the test I'm using that it's a false positive versus a true positive?

And so you never get rid of the false positive issue because no test is perfect. You never get rid of the false negative problem no matter what the incidence is because every - no test is perfect.

And so I'm sorry I can't give you a really cookie cutter applies in all situations answer. It's just important that if it really matters for the result, you know, it might be good to get a confirmatory test.

(Kotamudi Venkep): So just like how you recommended the serology test you have certain disclaimers. So do you mean these molecular tests should then also have to come up with these situations or the disclaimers?

Dr. Timothy Stenzel: We are looking at - Toby's working on an FAQ update as we speak. In fact I think she has sent me language to review and I haven't done it yet. You sent me language yesterday and I forget when. So we're going to try to further explain this.

And we may look at additional information in the intended use statement, especially when let's say asymptomatic claims are made about a test. So it really is situational. It depends. It depends. So what we saw is that - recently, is nursing homes - we're seeing a lot of positives. When we went and tried to confirm it roughly they were only able to confirm about half of those positives.

And they were shocked. They were frightened that the test wasn't performing. What I'm saying is the test performed. To my knowledge in those situation, the knowledge - the situation that I'm aware of I don't know that the test - I believe the test was performing as intended. It's just that this math says that, in a low percent population you're going to have false positives.

So don't - expect false positives in that situation. And therefore, if it's really important to know whether that patient is positive or negative get a confirmatory test.

(Kotamudi Venkep): Thank you very much for your…

Dr. Timothy Stenzel: I hope that's helpful.

(Kotamudi Venkep): …explanation. I appreciate it.

Dr. Timothy Stenzel: And - you're welcome. And the reason I enlist this audience of developers is that it can negatively impact what we do. If assumptions are made based on performance that's entirely expected that there's actually a problem. There isn't a problem with the test.

And it's - if someone views there's a problem with a specific test or a class of tests like direct antigen tests when there isn't, just became they have false positives, then it has potential for the public to not be supportive of the testing schemes that we want to roll out in order to help patients, especially those who are most vulnerable.

We all read stories of how SARS can go around a nursing home in no time flat. And everybody's infected including some of the staff. And that's what we're trying to prevent with some of the schemes that we're using. And not just us, but others. All right.

(Kotamudi Venkep): Thank you.

Dr. Timothy Stenzel: Next question.

Coordinator: And our next question is from (Dana Hummel). You may go ahead.

(Dana Hummel): Hi. My question is regarding the sale of COVID diagnostic tests to researchers for research use only. And I wanted to ask specifically, if there's

any restriction by the FDA to sell a non-EUA kit to a research lab for research only. I understand the FDA recommends the use of EUA kits at researchers but I'm wondering if researchers are allowed to purchase non-EUA kits for their research.

Dr. Timothy Stenzel: Toby, do you want to handle that question?

Toby Lowe: Yes, sure. So if it is truly a research lab doing research, then absolutely they can use research kits, research tests, research components. What we don't want to see is kits that are labeled for RUO being sold to a clinical laboratory for clinical use.

And we have discussed previously the guidance document that we have that talks about appropriate labeling for RUO and that is a really good resource to take a look at how we've laid out what is appropriate for an RUO labeled device versus a device that should be IVD labeled.

(Dana Hummel): Perfect. Thank you so much.

Toby Lowe: Sure.

Irene Aihie: We will take our next question.

Coordinator: And our next question is from (Win Lee Ju). Your line is open.

(Win Lee Ju): Hello. Thank you for taking the call. So I just have a question continue the discussion on the molecular test false positives. So right now it's very - I think it's very tricky here to determine the false positive because we don't really have a good reference panel. And what we do is just compare two molecular tests with each other.

So I could see one false positive or another one is just a false negative, you know? It's always hard to see which one is a true false positive or false negative. So what I found is that with a higher - this could be a problem with a very high CT value.

And so with that being said, the false negative can I say that false positive could just have more - could happen at a higher CT more and then just lower CT?

Dr. Timothy Stenzel: Yes. I think that may be dependent on the test and the platform and in particular, the (unintelligible) chemistry because if you have, you know, a baseline that say is set such to sort of maximize sensitivity that baseline can be inadvertently in a small, in a well-performing test a small number of cases, you know, that the baseline can be crossed earlier on too and just the case based on the detection of the technology.

So really my statement has to do with when you are - when you know you have a population that has a low percent positive, you know, and it's critical to properly - to know whether that patient is truly positive or not, in the - and the chance of a false positive is significant even with the test performing as intended, that's when I recommend that you take a look at confirming.

This is not a confirming all false negatives, potential false negatives and all potential false positives. That would be not workable. And but when you are interpreting results of any test yes, the clinician wants to take that into the context of the situation. So if you think this test is falsely negative I know that some of them are ordering a second test.

Or if they think it's falsely positive I know that some of them are checking to make sure. So this is - this - at least for some percentage of the clinical population of healthcare providers, they are taking this into account. I just think that due to recent news reports and other reports, there are elements of the healthcare system that we're trying to bring up to speed on in particular, interpreting positive results in a very low percent positive environment.

(Win Lee Ju): Yes. So yes, you see have a very low positive rate of prevalence then you can afford to check every positive. But if you have higher prevalence and also if the CT value are high in many people and then it's kind of hard to do that. And also, if you don't check them right away and that if you check like a few days later and that could just be that first time is real and the second time is still real but the virus just clear out. You know?

Dr. Timothy Stenzel: You're exactly right. You're exactly right.

(Win Lee Ju): Yes.

Dr. Timothy Stenzel: It's why basically every test that we've authorized to date is by prescription. Why is that? Because having a clinician involved, somebody who can order the test involved, they can help interpret the results correctly. Is it a perfect system? No. But even the direct antigen tests that are being used in nursing homes across the country are still by prescription only.

And so we are wanting to augment what we're saying the CDC has guidelines on this that are published on their Web site. And CMS and CLIA are supportive of this. We're going to augment what we're saying about this, to help educate the full community. And on this situation where there's a significant ratio of false positives in a population where it really matters.

And there's huge disruption if there is a positive and you want to make sure it's a true positive. Okay?

(Win Lee Ju): Yes. Yes. Thank you. So yes, just one last comment on that is so on this molecular test, unlike antigen tests or antibody tests, we all have those sensitivity specifically - or specificity test given to the public. But for molecular test there's no such thing given. I think it's harder to determine the specificity as you just discussed.

And because some clinicians - some physicians ask me what's the specificity of your test? Well if I look at the EUA and they all say well, this is highly specific or 100% specificity, it's really - but I know it's not. So is there any effort actually putting some - at least specificity for some of the sensitivity for our molecular test from this well known EUA?

Dr. Timothy Stenzel: Yes. So, you know, even in the early days when positive patient samples were not readily available, and we allowed a virus to be diluted into negative patient matrix, there was still negative patient matrix allowed. And our bar which is an EUA bar, it's not a typical FDA bar for a test, during a pandemic and this pandemic we allow as few as 30 negative patient - independent negative patient samples to be used in the validation.

In the IFU it's listed as negative percent agreement. That's for technical reasons because you don't have a - not a true comparator and we call it negative percent agreement. So if you look at negative percent agreement from the very beginning, all of - to my knowledge, all of the tests authorized have a specificity determination.

It however, may be on as few as 30 negative samples in which case the - in which case the confidence intervals around that result are quite large. And we

do provide the confidence intervals in the instructions for use with the test. So you can look at that confidence interval as well.

And that's another thing that's perhaps not well understood is okay, we're measuring the performance of these tests for this EUA and, you know, and the confidence interval is dependent in large part, on the number of samples that are tested. If only 30 are tested and you may be - you may measure 100% specificity or 100% NPA.

But, you know, statistics tells us that it could be lower than that and we provide a 95% confidence interval so that you can say oh, you know, a 95% confidence interval means you can fall as low as X% on the specificity based on the small sample number that you've tested in the validation study.

(Win Lee Ju): Okay. Thank you so much. Thank you.

Dr. Timothy Stenzel: You're welcome.

Coordinator: I would now like to turn the call back to Irene Aihie as there are no additional questions at this time.

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 Thursday, October 29. If you have additional questions about today's presentation, please email CDRH-EUA-Templates@FDA.HHS.gov.

As always, we appreciate your feedback. Following the conclusion of the 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 discussion.

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

Coordinator: And this concludes today's conference. Thank you for participating. You may disconnect at this time. Speakers, please standby.

END