

Virtual Townhall

Moderator: Irene Aihie

June 23, 2021

12:15 pm ET

Coordinator: Good afternoon, and thank you all for standing by. At this time, all participants' line are in a listen-only mode. After today's presentation, you will have the opportunity to ask questions, and you may do so over the phone by pressing Star 1 at that time. Today's call is being recorded. If you have any objections, you may disconnect at this time. It is my pleasure to turn the call over to your host for today, Ms. Irene Aihie. Thank you, 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 61st 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, Dr. Timothy Stenzel, director of the Office of In Vitro Diagnostic and Radiological Health, in the Office of Product Evaluation and Quality, and Dr. Kristian Roth, both from CDRH, will provide a brief update. Following opening remarks, we will open the line for your questions related to the development and validation of tests for SARS-CoV-2.

Please remember that during this town hall, we are not able to respond to questions about specific submissions that might be under review. Now, I give you Timothy.

Dr. Timothy Stenzel: Thank you, Irene. So, welcome again to this week's call. We continue to get

some really good questions pre-submitted, and we will respond to all cases - all questions, whether live here on the call or offline. So, if we do not mention your question, rest assured that either we've already sent something, or we will send something relatively shortly as far as a response to your question. And sometimes questions - some questions are best handled offline. We look for general applicability to these questions and rather than sort of specific questions.

I wanted to start off with some announcements, just some updates, and then move into the pre-submitted questions, and then into the live questions. So we continue to see SARS positivity rates fall in the US. That's great. We do continue to see the Delta variant increasing in the percentage of the positives, and it's - Delta variant rise is particularly in those who are unvaccinated, which, there are in some areas of the country, a large number of unvaccinated adults.

So, we're monitoring this closely, and hope all is well. But we're pleased with the overall rates falling, as we'll get into in some questions today, and, you know, there is some challenges when the rates are falling for test developers. I wanted to also expand upon those things that we're currently reviewing. So we've stated frequently our current priorities are still the same.

Did want to expand, so we will see new technologies be developed that could be helpful in this pandemic. And our stated priorities are not intended to cover those things that we don't know about, or are new. Our stated priorities largely revolve around detection of Immunoglobulins, the raise to natural infection for SARS or a typical serology test, antigen tests, and molecular tests.

So there are technologies that are new, novel, unique, and may come to bear and be helpful. And we recommend that you check with us through the pre-EUA process to see if it's something that we think would fall under the EUA review criteria and that we think has potential to impact in a positive manner, our pandemic response.

And I will call out one particular type of test now that is emerging, and we've heard about, and that has to do with T Cell assays. We have authorized already a T Cell receptor sequencing beta-receptor sequencing assay. That particular assay functions

largely in a way a typical serology assay doesn't in that we're looking at a T Cell receptor response to SARS-CoV-2.

There are other T Cell assays that are more looking at functional T Cell response, and those are the newer types of assays that we're hearing about. So, you know, I just want to state that these types of new technologies, want to hear about through the pre-EUA process. If we think there's potential, we want to work with the developers to work on an EUA submission.

And we are absolutely receiving these T Cell functional assays now for review, and do hope that ultimately they will pan out to be helpful, although I think there's a lot of open questions that remain. But we're committed to reviewing those right now.

I also wanted to talk about two other things. One is the use of international studies, given the falling rates of SARS positivity in the US right now, and conversions to full authorization. So, we're continuing to recommend those that want to remain long-term on the market, you know, this would be, you know, probably long-term in the future, that this would be necessary to stay on the market.

But we are encouraging the folks who want to go this pathway, to convert their EUAs to full authorization. We know that with the falling rates, this is challenging. When appropriate, we'll make full use of banked samples, in addition to prospective trials or rather studies, not trials, prospective clinical studies.

We are also now very open to the use of international studies to acquire positive samples. That's both for EUA and for conversions. So we've done this in the past when rates of positivity in the US are too low, or are relatively low and are very challenging to developers, such as pathogens such as Ebola, TB, malaria, dengue fever.

So we've done this in the past. And now that we are seeing falling rates in the US, we are more open to the use of international studies. We do want to make sure that they are done as we recommend. For example, if they're point of care tests, that the settings that they're evaluating in internationally, are truly point of care. We want to

make sure that the language requirements are there.

You know, non-US foreign language instruction should not be used to instruct non-US users of the test. And this applies - point of care can apply also to home tests if the appropriate settings are used for evaluating home tests. This is all in an effort to get actual positive patient samples for the validation, which is always preferable to the alternatives, which is why we're encouraging that now.

Okay. I think with that, we'll move into the pre-submitted questions. Let me just pull those up. So the first question has to do with the use of retrospective samples for antigen test validation. And in particular, the question was, can we use banked samples, banked frozen samples for OTC, over the counter and or home test applications?

And while we're - and I'll get to it. While we're open to using banked frozen samples for point of care validations, it's really, really challenging using home users to substitute samples. So, that's why I'm encouraging international studies when needed for home testing and or point of care testing if it's difficult to get the banked samples.

But for point of care, as I'll get into, there's a pathway and - or if you use this for a long time already. So, we do not recommend banked samples for home test validations, whether OTC or prescription use. We do want to see - we recommend fresh samples, as we're really looking at the lay user collection process here. So we want to know that home users can collect and also accurately perform the tests and get the right result to explain that.

So, for - as I said, for point of care, so we would want to see a full set of a minimum of 30 positives and 30 negatives with the frozen banked samples for a point of care claim. And then we would authorize that test if we saw a minimum of at least five prospectively collected positive samples with successful performance, in addition to the frozen samples.

So we do want a complete set of frozen samples so we can evaluate frozen samples

and sample type. And we're willing to authorize them with a minimum of at least five prospectively collected positive samples. And again, those can be international if needed. And then post-authorization, we would expect the study to complete a fresh sample prospective study, so that we have a complete set of fresh samples to understand performance and to continue to allow the test to be marketed in the US. Okay. I think that pretty much covers that question.

Okay. So, the next question has to do with pod pooling, and it doesn't specify whether those are antigen tests or molecular tests, point of care tests, or central lab tests. So, you know, antigen tests are particularly challenging for pooling due to the sensitivity requirements of pooling. So, that's - that would be important to have an offline conversation with our expert staff on antigen test pooling.

However, for media pooling or swab pooling, both are very - we're very open to that, to non-point of care molecular tests. And - because we think moderate to high complexity labs can perform media pooling. For point of care tests, we are recommending that you consider swab pooling, and we do not recommend media pooling in the point of care.

In that setting, with untrained non-laboratorians performing the testing, media pooling presents some inherent risks of a mix-up and cross-contamination that we do not feel that that - that the benefit-risk profile on point of care settings justifies media pooling. However, I think swab pooling is a great alternative, especially in the point of care setting, where you can then potentially relatively easily follow up with an additional swab for those pools that test positive.

Okay. Next question has to do with priorities, having to do with panel tests, particularly as we may see a rising prevalence of non-SARS respiratory viruses. We have stated our priorities for review currently where our position is focusing on increased testing, accessibility, and capacity. Panel tests have the ability to be more efficient, because we don't know whether it's SARS or some other virus, and you end up doing two tests versus one. That's less efficient. It uses more resources and supplies.

So we continue to prioritize high volume, multi-analyte devices, including, central lab, of course, but including point of care and home RX tests. We are not recommending multi-analyte tests for over the counter, which could very well include testing of asymptomatic. We just don't have any experience of using non-SARS tests in the asymptomatic population. But home RX is acceptable and is what we recommend if you're interested in a home multi-analyte device.

Next question is, if you have a home - a prescription antigen test, this would apply to molecular tests as well, can you limit it only to symptomatic individuals? Yes. So that's been the pathway so far. We know - we've heard from multiple commercial parties that there is value in having a prescription home test. And you don't absolutely need an over-the-counter test to access the home test situation.

And, you know, if you do your validation on symptomatic individuals in the US or ex-US, that's fine. We'll authorize the test. It will be the typical language of authorization that is, the patient is suspected of having COVID, and there won't be any claims about asymptomatic screening.

And then, of course, if in a symptomatic population, the performance is acceptable for our - serial testing and pooling - not pooling, serial testing pathway for getting any symptomatic screening claim with a PPA of at least 80%, or lower bound of at least 70%, you always have the option at that point after submission or in your submission, to ask for the serial testing claim. The serial testing claim is not required. And if you want a single-use home antigen or molecular test in the symptomatic population only, that's fine. We'll definitely take a look at that.

There was also a question related to the use of CT values to exclude patients in studies. We are still not recommending exclusion of test subjects based on CT values. There's multiple sources that say that CT values are not reliable enough to predict whether someone's infectious, for example. So, we are still not recommending use of CT values to exclude test results from the clinical study.

The next question includes topics of point of care gene expression. Chris has given thought to this question and has prepared a response. So, I'll hand it over to Chris for

responding to this question. Over to you, Chris.

Dr. Kristian Roth: Thank you, Tim. So this question is about a gene expression test that can detect SARS-CoV-2 and other viral pathogens, which is flu or RV, in addition to measuring the host response and generating a risk score. And the question is, would we consider this under EUA, and specifically similar to a molecular test?

I think that the challenge here, and this is assuming that the test just measures the human gene expression markers, is that these are two different intended uses. I think the diagnostic claim is one intended use, and then the risk score is a different type of intended use, perhaps at the patient management type of use. And so, those would be two different validation recommendations for those two claims.

If it hasn't been previously granted an EUA, which I'm assuming it hasn't, you know, we'd definitely like to discuss this in a pre-EUA setting. We'd want to know a little bit more about how the risk score is used for patient management. And seeing a robust study establishing the link between human expression markers and the infection for the diagnostic claim, also would be important to flesh out. And that's all for me. Tim, if you have anything to add.

Dr. Timothy Stenzel: No. Thanks, Chris. Okay. On to the next question. This question has to - the use of banked, prospectively collected positive samples, I mean, banked samples to supplement prospectively collected positive samples for molecular diagnostics tests. And so, here for molecular tests, there is this option to use banked samples.

So we do want to test validation to be performed in the point of care setting by point of care users. And we feel that they are expert enough to collect samples in general. So, we're not trying to test their ability always to collect samples, but we want to know, can they accurately perform the test, this novel test that hasn't been seen by them before? In a busy point of care setting, in their normal workflow through seeing patients testing and not testing.

So, we don't have similar restrictions on the use of banked samples. We would like to see an attempt at prospectively collected samples, and see some fresh sample

results. And then we do want to understand the details about the samples to make sure that they were collected and used and selected in an unbiased fashion.

Commercially banked samples are acceptable in this case as well, but we don't want, you know, we only high positives picked from that banked sample collection, and that - and typically, when you use banked samples, you want consecutively collected samples, including positives and negatives. Chris, I wanted to see if you have anything to add to this response.

Dr. Kristian Roth: No, I think you've covered it. Thanks.

Dr. Timothy Stenzel: All right, moving on to - this is a non-COVID question. Obviously this call - this weekly call, and much of our efforts publicly facing right now, are on efforts to assist the development of SARS tests that will aid our response to the pandemic. There are still a whole lot of test development in non-SARS areas.

The question has to do with, are we reviewing our regular submissions, you know, like 510(k)s? And then what about our non-SARS pre-sub, Q-sub, you know, what are we doing in that area as well? So, while previously, we had paused some non-COVID tests, including 510(k) submissions. We have now restarted all - completely all of those reviews as of June 10th.

And we do not intend to pause any more going forward, you know, barring some unfortunate events, of course. And however, we're still limited in our capacity due to the overall workload in the office to review many of the Q-sub and pre-sub.

So, you know, unless the IVD pre-sub is related to COVID, which we are reviewing, or companion diagnostics, which we're reviewing, or a breakthrough designation request and follow-up pre-sub for that, or it is determined in some other way being a highly significant public health impact, we are unable to review them at the time due to workload constraints.

We - and that's probably going to be the case for the remainder of the year. We are - do recommend that you take - if you're in this situation, obviously, if it's not

breakthrough request, in many cases, there are previous similar decision summaries that are publicly available, and we urge you, or recommend that you go look at those decision summaries.

The more recent ones are going to be potentially better to look at our most current thinking on validation of those tests, so that hopefully the vast majority or all your questions that might be posed in the pre-sub, can be addressed by reviewing those decision summaries.

All right, and I think that is the end of our - the questions that we were going to go over on today lives, or submitted previously. And we can move into the live question phase. Thank you.

Coordinator: Thank you. If you would like to ask a question, please ensure your phone is not muted, press 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 Sousan Sheldon. You may go ahead.

Sousan Sheldon: Hi, Tim. Thank you for the explanation. I am very excited to hear that you - and actually want to verify what I heard, that you are expecting - accepting usability studies from outside the US. Is that - did I understand that correctly?

Dr. Timothy Stenzel: So usability studies should be easily done within the US. It's the clinical studies where you need actual positives that we see the need in some cases where a sponsor has demonstrated they can't get prospectively collective partners in the US, that we would go outside the US. So, you know, you don't - Chris, correct me if I'm wrong, but I don't think you need actually, you know, truly symptomatic people to do the usability studies in the US. You don't need positives to do usability studies in the US.

So, you know, that's probably still very capable if you're in the US, but as far as the actual clinical studies, collecting positive or negative samples, particularly positive samples that they were unable to collect in the US, we do want to provide a clear pathway to you ex-US. Chris, anything to add to that, to correct if I'm wrong?

Dr. Kristian Roth: No, just agreeing. I think we'll find a way to facilitate these usability studies in the US because I think that's ultimately the intent of user that we really want to investigate. So, we will find a way, yes.

Sousan Sheldon: All right. So we do the usability studies still in the US, but there is no need for enrichment for positives. So if we get all-comers coming in for over-the-counter test, we get what we get, and that's acceptable with the usability study as far as submissions are concerned, correct?

Dr. Timothy Stenzel: That sounds correct to me.

Sousan Sheldon: All right, thank you very much. Thanks, Chris, for the explanation. I'm done. Thank you.

Dr. Timothy Stenzel: Okay, thank you.

Coordinator: And our next question is from Franco. You may go ahead.

Franco: Thank you. My question is related to - excuse me.

Dr. Timothy Stenzel: I can hear you. Go ahead.

Franco: Okay. So my question is related to a lateral flow test, a qualitative lateral flow test that targets the spike protein and can be used on vaccinated individuals. So, we've been doing some playing around with this test, and we've noticed that on people that have been vaccinated with Moderna, Pfizer, and even some folks that have participated on the Novavax trial, the Phase 3, that the test is actually able to detect the spike protein, thus giving you a, I guess you can call it a positive result.

So, it's a purely qualitative test two line. One is the control on one of the test line. Would - and the idea would be that these tests could be used at point of care, not at home, even though they are a finger prick. Is FDA amenable to something like that?

Dr. Timothy Stenzel: So, I think you're talking about serology tests. And so, currently, we do not know really the hallmarks in a serology test of actual protection and/or immunity, whether it's natural infection or following a vaccine. So, the studies are relatively easily done to show that given test can detect positive reactions, positive immune responses to infection and/or vaccines.

However, until we really understand what it means to have a positive test post-vaccine, and those studies are ongoing, US government-funded studies. And we hope within weeks or months, we'll have that data. That data, we believe, will be made publicly available very soon after the results are known. And the FDA is very eager to see that information as well.

It's at that point that we would entertain in - and we recommend that developers pause with us in their development work to see what that means. It may be that a fully quantitative result is needed. We think that's likely the case, based on other post-vaccine tests we've authorized for rubella, where we know the sterilizing level link to international units for rubella.

And so, we believe that it's probably going to- we hope that's going to be the case for SARS. We do believe it's going to be similar to rubella and other such vaccine tests, that it's really quantitative result linked to an international standard, is going to be the way to go, and able to provide useful information to clinicians based on serology testing.

You know, all of this is still up in the air, though, because we don't know what the data is going to show on these studies. And so ...

Franco: So it's just ...

Dr. Timothy Stenzel: ... really for serology tests, we're looking for two things. One is this clinical relevance that's being addressed by these studies. And then second, we will ask for testing of, at least in the US, for US authorization, a minimum number of positive - of baseline negative serology tests prior to vaccination, with each of the authorized vaccines. Currently, there's three authorized vaccines.

And then likely in the neighborhood of four weeks post-vaccination for each of the vaccines. Obviously one individual is not going to get - usually not to get more than one of the vaccine. So, for each of the three currently authorized vaccines, we'd be recommending at that point, just to give everybody a flavor of what we're going to be asking for, a baseline just prior to vaccination, showing a negative result with the candidate serology test.

And roughly, we think their conversion is going to be somewhere around four weeks post-vaccination, post the last dose. So if it was a single-dose vaccine, four weeks after the first dose of that dose vaccine, or if it's a two-dose vaccine, it's four weeks after the second dose. That's, unfortunately, the most we can say right now, barring additional information that comes in through these very pivotal studies.

Franco: So, let's say, let's just wait.

Dr. Timothy Stenzel: Yes. We're in the waiting pattern. We have made a statement about the use of serology results, and I'll refer you to what we are recommending to clinicians as far as using current authorized serology tests in their clinical practice. So, we're not - and I would refer you to that. We're certainly not getting into the business of eliminating the practice of medicine.

So, the only thing we recommend is that you know what you're doing, you know, if you're a clinician that you're here. And, you know, all the three vaccines that have been authorized in the US are spike protein vaccines. So, you probably shouldn't be using an N-protein serology test, and following up after vaccination if that's okay.

Franco: Yes. And I think it's very important that you bring up the N-protein antibody test. So, clearly, I'm not talking about that. I'm talking about a test that is targeting the S-protein, not the N-protein.

Dr. Timothy Stenzel: Of course, yes. Although clinicians can - I know this isn't in current serology labeling that they can choose to say, I want to know the patient who is now vaccinated ever had, you know, an infection, a natural infection.

And so, a combination of a spike protein serology test and separately ordered N-protein tests, could potentially inform whether it's just a vaccine situation, or it may have been vaccine and natural infection in their history. And again, we really want to wait the clinical outcome studies following vaccination, or natural infection.

Those studies are ongoing, but most studies are focused on post-vaccination responses, and see what all that means and what criteria may be needed to understand and truly identify. It could be that, and particularly say in immunocompromised individuals, that a low level of an antibody response is not protective at all.

So, we just need to understand that better before we can - we just need to understand that at all before we can go forward with that. But that's what we recommend there. All right. I think we probably ought to move on to the next caller, if there is one. Thank you.

Coordinator: And our next question is from Elliot Rosen. You may go ahead.

Elliot Rosen: Hello. Thank you for taking my question. If you don't mind, I actually have two very quick questions, and these are both regarding the templates for test development in serology tests detecting or collating some neutralizing antibodies. And the first one is regarding validation of the comparator assay.

We're asked to use 75 samples collected prior to December 2019 that are SARS-CoV-2 negative. And we are wondering, if one clinical agreement study involves the collection of serum samples, is there any issue with our validation for our comparator assay utilizing plasma samples or some combination of serum and plasma?

Dr. Timothy Stenzel: You know, I'm not a neutralizing antibody expert on the PRNT for the gold standard. Chris, maybe you can help me out on this response. And I don't remember if it's plasma or serum that is used on the PRNT test, but that is the gold standard. That's what we do recommend that you validate for a comparison study.

And I just don't remember the sample type. Whatever the appropriate sample type is - scientifically known, is going to be allowable for our reviewers. And, you know, we just recommend those banked older samples because we know that there's not going to be - they're not going to be confounded by potential exposure to SARS. Chris, do you have anything to add to that?

Dr. Kristian Roth: Yes, not really. I think the claims, if you're going to use the comparator method with a matrix that's not claimed, that's something that I think we have to have further discussion on. And as far as the specifics between plasma and serum for PRNT, you'd have to defer to our serology folks.

Elliot Rosen: Understood. Thank you very much. The other question just very quick, and you've already addressed it a bit, we are starting to collect samples for this trial, and we have noticed due to declining incidents, trouble enrolling subjects to obtain samples from.

And I know that you said that the use of retrospectively previously collected samples is all right, but is there an issue if we were going to modify our protocol mid-trial to make it so that maybe half the samples we collected are collected prospectively from active subjects, and the other half were to be collected from retrospective samples that were previously collected. Is there any issue if we change our trial and operate that way and have a combination of both?

Dr. Timothy Stenzel: So this is a serology test validation?

Elliot Rosen: Yes, this is for - not for the validation, for the actual clinical agreement study for neutralizing antibodies.

Dr. Timothy Stenzel: Yes, the clinical study. So, no, this is a - it is a challenging area, and with declining positivity rates, which we've depended on previously, the molecular comparative results fortues, and then, you know, looking at time after molecular positivity. As the positivity rates fall, as vaccination and natural infection rates rise, this becomes more of a challenge to do the clinical study validation for serology tests.

So if you're - if you've tried prospectively collecting samples, and you're having trouble, then consider international studies that I alluded to, or I discussed earlier on the call, where infection rates are higher, if that's useful. Eventually, though, we know that we will have to - we will - you know, it will be important for us to move forward in some situations with an EUA or other fully authorized serology test comparator situation.

It's probably likely to include testing with probably three comparator tests, not just one, in order to determine what the status is. So, we're trying to hold off on moving to that, but we know at some point that's going to be something that, you know, will be entertained.

So, if you've given it the college try prospectively in the US, and if for a reason non-US samples are not accessible to you, come in to your reviewer and propose a three serology test comparator method to determine "truth, untruth" in the serology test validation situation. Chris, anything to add on that?

Dr. Kristian Roth: No. I'm getting some feedback here, though. If you send in those questions via email, we can get you a little bit better answer, or a more specific answer to this.

Dr. Timothy Stenzel: Rather than - okay. Rather than through a pre-EUA. So, just email questions. Okay. All right.

Elliot Rosen: All right, thank you very much.

Dr. Timothy Stenzel: All right. We'll move on to our next caller. Thanks.

Coordinator: And before we go to the next caller, if you would like to ask a question, please unmute your phone, press Star 1, and record your first and last name when prompted, so that I may introduce you. Our next question is Amy Wright. Go ahead. You may go ahead.

Amy Wright: Hello. Thank you for taking my question. My question again is about the clinical studies with the low positivity rate, and being able to get data from other countries.

So, in the past, when we had this problem, when we discussed this and the question was asked, there was a need to provide justifications for how that data is representative of the population of the United States. Considering the conditions now, do we still need to provide that rationale or that justification?

Dr. Timothy Stenzel: We want to know, because you have a choice of selecting where you go to do the clinical study to collect positives and intervening negatives in that study. We just want to know the setting and the user is as close to the US user as possible. So, if it's a point of care test, the setting should be in a truly point of care setting, and not a central lab setting trying to mimic the point of care.

And the users we expect are going to be non-laboratory end users. They're going to be, you know, healthcare workers likely, but not trained laboratorians. And the instructions we need to be in English. And if English is not their native language, that's okay, as long as they can understand English. But we don't want test developers to be providing them with some language other than English or Spanish in the instructions.

So, and it's only if you provide English and Spanish, obviously English is prominent, but if you also have a Spanish language in your point of care testing and you want to use that in the US, that's fine. And then you've got a primarily Spanish-speaking population for the study. But it's also true for home use. We just - we want to test as closely as possible to the US population, so that when the test is used in the US, we, and purchasers of the test, have a good indication of how it performed in the US population.

So that's why - I don't know that it's so much justification as to explaining how you selected that and that it applies, that it closely applies to the US situation because you selected the right language speakers, you selected the right users for evaluating the test in the right settings for that.

Amy Wright: Okay. So it will just be supplemental, because we do have a clinical study joining right now. It's just that we've been having difficulties obtaining more positives and also low positives. That's been our challenge is getting the lows positives with high CT values.

Dr. Timothy Stenzel: Yes. So, with the molecular test, we can entertain dilution. That's harder on an antigen test, so ...

Amy Wright: It's an antigen test.

Dr. Timothy Stenzel: So, we totally understand, you know, and we've been more flexible recently when positivity rates were so high in the US, and coupled with the fact that we had seen many developers do OUS test validation and not in the right populations where it was problematic, and we just wanted to get a better handle on how it will perform in the US population.

But now, we'd much rather use real patient samples from outside the US and in the optimal settings outside the US, rather than the alternatives to real samples, okay?

Amy Wright: Okay. Thank you.

Dr. Timothy Stenzel: It's all balancing benefits and risks, constantly adjusting that balance equation. Thank you.

Amy Wright: Okay, thanks so much.

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

(Kodumudi): Good afternoon. Thanks for taking my call. I am (Kodumudi) from (inaudible). My call is regarding the priority for serology tests. I think one of the priorities, the high throughput serology testing, I just would like to hear, because I have seen recently that are approved, most of them are automated tests. So is automated - is preferred as the high throughput or what really is defined as the high throughput in terms of how many number of samples per day or something like that. If you can just give your definition of high throughput, that will really help. And then based on that, we can plan our assays, that it meets those criteria. Thank you.

Dr. Timothy Stenzel: Yes. So, for a particular test, we've said you could find probably an even better

way to handle this, and details about your test, and whether you would qualify for high throughput. High throughput only pertains to central lab tests, those tests used in high complexity and your moderately complex labs.

We do also have criteria for high manufacturing capability. So, all of this is aimed at prioritizing at this point in the pandemic, those test reviews for EUAs that will substantially increase our emergency response capability. And low throughput central lab tests, or low manufacturing capacity of any test, is simply not going to substantially add to our response capability in the US.

And we can't justify it given all of our other healthcare IVD priorities right now, as I talked previously about putting non-COVID files on pause, putting non-COVID - some - many non-COVID pre-sub on pause just because of capacity. Again, it all comes down to benefit-risk. If we dropped everything and looked at absolutely every SARS test, and we didn't look at the new stuff, then cancer patients and other infectious disease patients would suffer.

And we've constantly, in this world, are trying to balance things for public health purposes. We've authorized almost 400 unique tests across serology, antigen and molecular. And there is a – substantial, already a substantial capacity. EUA provision is still open, though, and the FDA has flexibility to say what they're - what is currently of need for the public health emergency. So, again, specific questions about specific assays, whether it meets the high throughput threshold for central lab tests, you know, the email box is probably the best way to answer that question.

And then point of care test or home test, those aren't high throughput tests. But we expect that they're able to be manufactured at this point in the pandemic in high volumes, so that the review time and everybody's time involved in developing and reviewing this test, is worthwhile and really adds to our national capacity for COVID. So, okay.

(Kodumudi): So if I understand the definition of high throughput is not just a simple word, but you kind of have multiple things that is done that you would determine whether it is a high throughput or not. Is that right?

Dr. Timothy Stenzel: So we - yes. So we look at the particular test, and then automation for high throughput obviously helps. It's much harder to do high throughput manually, but there is a possibility of manual tests in high throughput. And our - we have not currently announced those thresholds that we use and which, you know, at some point in the future when we think things have settled down, and are somewhat more routine that we may announce those thresholds.

Once we do, they're kind of fixed. It's hard for us to adjust them as the pandemic proceeds. And we would - we still want that flexibility to adjust as current needs, you know, need to be met, and looking at our overall workload. Again, I think it's best handled one-on-one for the developer through our email box who will advise for high throughput.

(Kodumudi): Thank you.

Dr. Timothy Stenzel: Thank you. And what qualifies for high manufacturing capacity. Okay. If there is another question, it might be the last one given our time, we can move to that.

Coordinator: Our next question is from Christopher Patterson. You may go ahead.

Christopher Patterson: Hi. How are you guys doing? Thank you. My question is related to the antigen tests that are performed in direct assay comparator device validation. So the CT value is obviously a pretty important part of the submission, and I was just wondering if there's some sort of prescription for us developers of what kind of data we should provide regarding that specific comparator to validate it as capable of giving accurate CT values? Does that make sense?

Dr. Timothy Stenzel: Yes. So we use CT values for antigen and molecular test reviews, to make sure that there's sort of a balanced viral load in the clinical study. And it's not all at the very high level of viral load, which is not typically a natural spread of results in a prospectively collected study. You know, and it's our way of ensuring that we see a full range of expected viral loads for the time period looked at, and we see very low - very high CT, very low virus amount sometimes, and even in the early days. Most

likely, that's related to sample collection and not actual patients, but ...

Christopher Patterson: Absolutely, I agree.

Dr. Timothy Stenzel: So, our recommendations for the comparators, the high sensitivity central lab tests, we would - that's EUA authorized or fully authorized, there's only one of those right now, and with an extraction step in it. So some of the direct assays that don't have an extraction step - many of the point of care assays don't have an extraction step. We're, really - you know, we use a combination of the end use for the FDA reference panel results and or, you know, going forward, we may take a look at some other factors.

Do check with - through the email - templates email, whether the - that the comparator you want to use, is an exceptionally high sensitivity comparator or possible bank samples from your clinical study in case additional comparison testing may be needed.

We've seen some uncommon but helpful situation where going to bank samples have helped developers. But the best thing to do is to pre-clear that and go through the email - template emails address box, whether your comparator is appropriate. And we've basically said it was appropriate sensitivity and it's CT-based and that we'll accept those CT results, looking for the spread of positivity in your study, and making sure that there's sufficient number of low positives so we know the performance.

Christopher Patterson: Okay. May I - just a really quick follow up to that because, yes, absolutely, we did all of that. And so, the question is more, the CMS for the high complexity, their requirement is a qualitative test, right, is kind of their standard, just a positive-negative on the CT. That's their validation procedure.

But I guess my question is more, should we work with the laboratory or the comparator device to further enrich that, let's say, in LOD, or maybe some sort of standard curve study as well on our specific device and thermocycler? Or can we just trust in the IFU of the original manufacture?

Dr. Timothy Stenzel: You know, we haven't authorized any truly quantitative molecular test.

Christopher Patterson: Yes, that's okay.

Dr. Timothy Stenzel: We're not seeing a clinical need because - and there have been multiple non-FDA opinions, professional guidance that has stated that even if you have what's really quantitative molecular tests, there is huge variability in sample collection and sample transport that exists with respiratory samples, that doesn't exist for other truly quantitative molecular results like for HIV, HPV, HCV, CMV, where it's typically immuno blood-based sample which is well mixed in the human body, and gives us truly quantitative results that we can rely on in making treatment decisions. Are they responding to therapy or are they not? And they developed - potentially developed a mutation in HIV. That's currently embedded in current therapy.

So, respiratory samples are just challenging. We're not encouraging the development of truly quantitative molecular tests, because we are not aware of the clinical situation, or this really would require that. We always remain open-minded, though, just not encouraging it, okay?

Christopher Patterson: Yes, agreed. Thank you. Yes.

Dr. Timothy Stenzel: All right. I think that may bring our call to a close, I think.

Coordinator: Right. And this concludes the question-and-answer session. I would now like to turn the call back over to Irene Aihie.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions during today's town hall. Today's presentation and transcripts will be made available on the CDRH Learn web page at www.fda.gov/training/cdrhlearn, by Wednesday, June 29. If you have additional questions about today's presentation, please email cdhr-eua-templates@FDA.HHS.gov.

As we continue to hold these virtual town halls, we would appreciate your feedback. Following the conclusion of today's virtual town hall, please complete a short 13-

question survey about your FDA CDRH virtual town hall experience. The survey can be found now on www.fda.gov/cdrhwebinar. Again, thank you for participating, and this concludes today's virtual town hall.

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

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