# 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 participants are in a listen-only mode until the question-and-answer session of today's conference. At that time you may press star 1 on your phone to ask a question. I would like to inform all parties that today's conference is being recorded. If you have any objections you may disconnect at this time. I would now like to turn the conference over to Irene Aihie. Thank you. You may begin.

Irene Aihie: Thank you. Hello. I am Irene Aihie of CDRH's Office of Communications and Education. Welcome to the FDA's 40th 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 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, and hello everyone. And welcome back to our town hall today. I'm going to start off on a somber note, a remembrance for a pioneering COVID test developer who we recently lost. So Dr. Andrew Brooks was a Research Professor at Rutgers New Brunswick School of Arts and Science in the Department of Genetics. He also led the creation of the first EUA-authorized saliva based test and the first home collection of saliva. And reportedly, reported in the news now, at least on the Rutgers site, more than 4 million of those tests were performed between authorization and now.

So it's really sad to see somebody who was able to advance testing in this way to be lost to us. He passed unexpectedly on Saturday and leaves his wife, Jill and three daughters, Lauren, Hannah and Danielle. Sorry. It's been a long fight. Anyway, we're very thankful to him for his work. And we'll remember him always.

Okay pull it together Stenzel. I wanted to give some heads up on mutations. This continues to be a very hot topic and, you know, I think it's ideal for those that already have an EUA-authorized test and those who are developing tests, to consider the variants.

We move to authorizing single target assays relatively early in the pandemic with the knowledge at that time that single target assays - we had not seen mutations that would impact them. But we are starting to see mutation to impact tests and obviously single target versus multiple target - targeting

multiple reasons of SARS virus and, you know, there may be a performance difference going forward.

So we'll certainly stay vigilant at the FDA's side on monitoring this. But we do want to put a shout out to developers to certainly be considering this. And they - as - when they, you know, and to work with us as - in looking ahead in how we can maintain the highest performance possible, for COVID tests, for molecular tests that includes probes and primers.

We're obviously open to talking to developers who want to make updates or that are in development, you know, about how best to do this. So no change in recommendations at this time. Just, you know, a heads up. We think that antigen developers and serology developers should keep these variants in mind as well.

You know, numerous of the serology tests do target the spike protein which can alter and at least one of the antigen tests does target spike protein. But of course, there can be a mutation that could affect other genes, other targets within the virus. So with that, we'll go into questions. Thanks so much.

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

Coordinator: Thank you. We will now begin the question and answer session. If you would like to ask a question, please press star 1, unmute your phone, and record your name clearly. Your name is required to introduce your question. If you need to withdraw your question, press star 2.

Our first question comes from (Hannah Gabrielli). Your line is now open.

(Hannah Gabrielli): Hi. Thank you for taking my question. So I came up and asked a question a few weeks ago about breath tests that we're developing. And I wanted to thank you for your answer then because I actually received a recommendation for breast test developers and resubmitted a pre-EUA according to those considerations. I wanted to ask today, because this is something that I haven't found anywhere, what is the required sensitivity that you are asking for breath screening for COVID and respiratory viral infections?

Dr. Timothy Stenzel: I'm sorry, I didn't catch that last part. What is the what?

(Hannah Gabrielli): What is the sensitivity that you require - you are requiring for breath test screening or…

Dr. Timothy Stenzel: Yes. Yes. So this is an important question and in fact, our team - I've charged our team with coming up with targets for this. They promised me today and - but probably by the end of the day, and…

Toby Lowe: But we haven't received any feedback yet though.

Dr. Timothy Stenzel: So, you know, you could imagine - and I'll just, you know, talk a little bit philosophy on a nonstandard sort of test. First of all, we're very open to novel tests. We have no idea if breath tests, you know, truly can perform, but we're totally open to it. We do want to have them validated appropriately and since they're a newer technology we're likely to ask for more than sort of the standard technology samples.

So I don't know if they gave you sample numbers yet. But we're working on them as well. You could imagine that the breath test might be used for either diagnostic purposes and/or asymptomatic screening, surveillance. You know, the FDA data for this pandemic we don't intend to regulate for surveillance.

So the other thing about breath tests because there may be other breath test developers out there, is that we are concerned with potential carryover from one patient to the next.

So that will be an important consideration of the safety and may not be in the recommendations yet. But I think there's going to be challenges with whether a developer wants to pursue, you know, symptomatic claims or asymptomatic claims. You know, some - there is some thought. Just to be open that, you know, we don't know if symptomatic or asymptomatic claims are necessarily the best claim to go to first, because some of the symptoms, you know, ideally might need a, you know, a test that has a longer proven track record.

On the other hand, we have a huge need to expand testing into the asymptomatic in screening population. And so that might be the more ideal population. I - there's no, you know, we're open to all comers here. So if you want to come in and you want to pursue symptomatic claims, we'll look into what that looks like. But I do see the sweet spot potentially for the technology - if it can perform, in the asymptomatic population.

And that it could really address some of our needs to really increase the - not only the amount of testing but the frequency so that everybody can get tested at will. So we'll want to look at in that population - in whatever population, we'll want to look at, you know, what is the sensitivity or PPA relative to a molecular test.

High sensitivity in molecular test and also the specificity and/or NPA. So does it call any false positives? Now, you know, it could be that for benefit risk calculations we may, you know, decide that positives should be, you know, double checked with the molecular tests and so that is some of the thinking that we're looking at right now. However, if the NPA is - I mean if

the PPA and NPV, negative predictive value, is extremely high for say people in the asymptomatic population, that could be - that could really be a win.

And so I'm just thinking through all the calculations right now. So I think we're going to ask for more positives and more negatives than we typically had. And we're working with our statistician on determining what that - what our recommendations are going to be there. So stay tuned. I think we'll be able to update our thinking hopefully by next week so that we can share with developers our latest thinking on that.

(Hannah Gabrielli): Thank you so much.

Coordinator: Our next question comes from (Josh). Your line is now open.

(Josh): Hi. Thank you for taking my calls. My question is what would be the process if like a developer of an EUA-authorized molecular test wanted to make a change to the primer and probes, perhaps in response to a mutation or perhaps proactively to make the - a test more resistant to mutations by adding a second target. Would that have to be like a whole new application that would have to go into the queue or an update to an existing one? Or what would be the process there?

Dr. Timothy Stenzel: So it would be potentially a supplement. It kind of depends on what you're going to do with the original test. You know, if you're going to take it off the market when you have a new authorization then there may not need to be a separate authorization. We're going to want to look at how the changes affect your accuracy.

So and you can imagine different ways to account for a mutation. You could use degenerate primers and probes and we would just want to make sure that,

you know, however you design those doesn't decrease the sensitivity of the overall reaction. There might, you know, there are different ways to go about that.

And then if you are adding a new target, we want - we do want to make sure that that target is going to be accurate. We know the level of that accuracy. And so that would be, you know, pretty much all the key elements of development which would be, you know, if it's just for symptomatic claims then, you know, 30 positives, 30 negatives in LOD. And the - in the cross-reactivity and inclusivity testing that we ask for.

(Josh): Okay. And so it sounds like if you wanted to get - you were to take the existing test off the market and replace it, that it could potentially be a faster review process rather than submitting a brand new application?

Dr. Timothy Stenzel: You know, if somebody is trying to improve the safety due to the variants, we're going to make that a priority review. So I think that's something that we haven't set as a formal priority, but very clearly that's important.

(Josh): Okay. Thank you.

Coordinator: Our next question comes from (Sitrali Kulani). Your line is now open.

(Sitrali Kulani): Yes, hi. We're developing an antigen test, lateral flow. And I just had a question about combining a prospective study and a retrospective study. So if we follow what's on the EUA, like provide retrospective samples and then along with five positive prospective we collected, is that considered okay, especially for a point of care claim?

Dr. Timothy Stenzel: That's our current thinking. Yes. So…

(Sitrali Kulani): Okay.

Dr. Timothy Stenzel: …then there would be a post-market commitment.

(Sitrali Kulani): Yes.

Dr. Timothy Stenzel: If everything looks good and we can authorize there would be a post-market commitment to figure out…

(Sitrali Kulani): And then do we have to provide any fresh negative samples?

Dr. Timothy Stenzel: Yes. So if you're going to do a prospective collection of five fresh samples you're going to - you're also going to collect negatives in that. So, you know, that's - that shouldn't be any problem for you…

(Sitrali Kulani): Okay.

Dr. Timothy Stenzel: …to collect, you know, the 30 - the 30 negatives…

(Sitrali Kulani): Yes.

Dr. Timothy Stenzel: …or whatever the minimum negatives is pre-market.

(Sitrali Kulani): Okay. So for negatives, mostly you'd want them to be covered pre-market and then post-market be mostly on the positive?

Dr. Timothy Stenzel: Yes. We don't think that's going to be too burdensome…

(Sitrali Kulani): Yes.

Dr. Timothy Stenzel: …because…

(Sitrali Kulani): Yes.

Dr. Timothy Stenzel: …the negatives are going to be relatively prevalent. It's going to be the positives that you'd going to have to wait on. So, you know, I would just, you know, set up your clinical study and collect all the negatives…

(Sitrali Kulani): Yes.

Dr. Timothy Stenzel: …or that you need or that you're doing in your study, along with looking for the first five positives.

(Sitrali Kulani): Okay. And then on the EUA application we would just state that we have an ongoing prospective study?

Dr. Timothy Stenzel: Yes. Yes. You could let the team know that you're working on getting those prospective fresh samples.

(Sitrali Kulani): Okay. Thank you.

Dr. Timothy Stenzel: You're welcome.

Coordinator: Our next question comes from (Kirsten Banker). Your line is now open.

(Kirsten Banker): Thank you for taking my question. I was just wondering what is the role of (tunnel) government service staff in the review of EUA applications and how this affects the FDA's review process and the target review time.

Dr. Timothy Stenzel: I'm sorry. Could you ask that question again?

(Kirsten Banker): Oh, sure. So I was just wondering about the role of the (tunnel) government service staff in the review of EUA applications and how this affects the review process and review timelines.

Dr. Timothy Stenzel: I think you may be referring to some contractors who we've hired to help with reviews. So we - the latest surge doubled. Prior to the surge we had brought on contractors and then, you know, more recently we with internal resources within the center at the FDA, we doubled the resources on COVID. And so all of those additions have allowed us to make a lot more decisions more quickly.

Now some of those decisions aren't always positive decisions and we certainly don't advertise and post negative decisions unless we're removing something from the market.

(Kirsten Banker): Okay. Thank you.

Coordinator: Our next question comes from (Kay Taylor).

(Kay Taylor): Yes. Thank you and your team for the opportunities these town halls provide the attendees. My question is regarding clinical trial defined for at home antigen tests. In particular, my question is the collection of the nasal swab samples for both the test device and the reference PCR device. The test sample device, nasal swab, would be self-collected by the representative at home user and the reference device sample would be collected by a healthcare professional.

Does FDA have guidance on the order of the collection, meaning should the order of the nasal swab collections be randomized, or would FDA expect the self-collection to occur for the test device first, and then always followed by the healthcare professional collecting the swab for the reference PCR test?

Dr. Timothy Stenzel: Yes. So again, are they both nasal - anterior nasal swabs?

(Kay Taylor): Yes.

Dr. Timothy Stenzel: Okay. So, you know, the sort of ideal, you know, ivory tower sort of answer and then I'm going to give you the more practical and the answer that I think is best to follow and the fairest relative to the candidate device. So this is fairly simple although hopefully, I don't mangle the directions here. But yes, you do want to randomize. Okay? But you also want to make sure that the candidate device isn't at a disadvantage here.

And a number of studies have been performed this way and we don't think standard of care is being significantly high on just the comparator test is, as we requested, you know, is a high sensitivity molecular assay with a separate extraction set-up. And we, you know, we urge people to look at our FDA reference panel data to identify, you know, the assays that are high sensitivity.

Then what you do is this can be - this is self-collected though, isn't it? Oh gosh. All right, this - this is a challenge. I haven't gotten this question before. How do you randomize a self-collected swab? How do you not bias the self-collector with this? You know, does it have to be a healthcare professional who's doing both swabs or one swab? Or can it be the candidate - can it be the patient candidate that is collecting both swabs?

(Kay Taylor): We presumed with the reference PCR test, that we'd have to follow the instructions for use which typically call for a healthcare professional to collect.

Dr. Timothy Stenzel: All right. So you're not using an at home kit. Not using an at home kit for this.

(Kay Taylor): Correct.

Dr. Timothy Stenzel: You're bringing them - okay.

Toby Lowe: So - but you're asking about whether the - this is before home collection that you'd be trying to validate. Right?

(Kay Taylor): Yes. So the test device would be an at home antigen test but the reference comparator would be a professional use…

Toby Lowe: Right. Okay.

(Kay Taylor): A professional use PCR test.

Toby Lowe: Right. I think we typically ask for the layperson collection to go first so that the, you know, the trained user isn't inevitably training the layperson on specimen collection.

(Kay Taylor): Okay.

Dr. Timothy Stenzel: The challenge with that is the patient collects the swab first in both anterior nares, which is typically the procedure, right? You could leave less -

significantly less virus in the anterior nares for the candidate - for the comparator test.

Toby Lowe: This would introduce bias there.

Dr. Timothy Stenzel: Yes. So I've been typically thinking of having a - this be a dual self-collection procedure. But when your comparator is one that doesn't have a self-collection option that presents a challenge. I think it's best that we…

Toby Lowe: …be a delay. I'm sorry.

Dr. Timothy Stenzel: Yes. You could collect after - again, after a period of time. So you could sample - the patient can sample their anterior nares first and wait a period of time. And we've - we have discussed this months ago with the RADx program and - about how they might do this. And we talked about some time periods but we didn't know what the best time period was.

One would be 15 minutes I think, up to an hour. So that would be actually probably the best way to do this is to, thank you Toby, for reminding me of that previous discussion on this topic. So that is one clear option. If that option doesn't work for you I think we're going to have to take this offline and think about this more.

So I would approach either your current reviewer or send a question into the Templates email box. But that would be the best way to do this. We do allow - if it's a single individual, is - wants to collect both random swabs at the same time, the swab - one swab swabs one nare, you know, their nare. And the other swab swabs the other nare and you swap and do the second collection in both nostrils.

And then you randomize which swab goes to which test. But in this case, and Toby's right, we're trying to not train the user and if you randomize 50% of the time you potentially would be informing the user. So - or if you're trying to examine the swabs and training them during the other procedure. So those are the options. If you want, I think the first option is - have a wash up or a restoration period…

(Kay Taylor): Okay.

Dr. Timothy Stenzel: They do the self-test then have them wait around for a period of time, probably no less than 15 minutes, probably an hour. But we have no data to support that time period, just that we want you to delay. So you probably ought to double check that delay with our review staff. Okay?

(Kay Taylor): Okay. Thank you, Dr. Stenzel.

Dr. Timothy Stenzel: Thanks, Toby.

Coordinator: Our next question comes from (Katherine Miranda).

(Katherine Miranda): Hi. Thank you for taking my question. My question is about sample collection. And we would like to know if an EUA-approved molecular diagnostic test is authorized for nasal swabs. Do the nasal swabs have to be collected by a healthcare provider or can they be self-collected in a healthcare setting under the direct supervision of a healthcare provider?

Dr. Timothy Stenzel: So it depends on the authorization of the EUA test. When we use it as a comparator it's important to use it as instructed in the IFU and not to go off label. If you have to go off label we would need to look at, you know, whether that was an appropriate modification and may need some validation

data depending on the modification. But it does present us - it would delay our review if you're not following a comparator assay as instructed. At the very least. And I can't promise that we would allow it.

(Katherine Miranda): Okay. Thank you.

Coordinator: Our next question comes from (Elaine Allen).

(Elaine Allen): Hello. Thank you for taking my call. My question is in relation to in our EUA application we have met the minimum EUA requirements which include samples from US donors only. We are expanding our clinical agreement study now to include outside the US samples. Would you accept that data that includes OUS samples, whether that is for the post-EUA data update or if we submit an amendment to our data in the IFU?

Dr. Timothy Stenzel: Remind me again about your device. What is it specifically and is it a point of care device?

(Elaine Allen): It is not a point of care device. It is ELISA, serology ELISA.

Dr. Timothy Stenzel: Okay. Well it's probably amenable for testing it at the NCI. So, you know, we do initial reviews…

(Elaine Allen): I'm sorry. Amenable for what? I'm sorry.

Dr. Timothy Stenzel: Oh…

(Elaine Allen): Can you repeat the…

Dr. Timothy Stenzel: …so it's ELISA for serology or for antigen? What is it?

(Elaine Allen): Serology.

Dr. Timothy Stenzel: Serology. Yes. So the ELISA test can be tested at the NCI, at the intergovernmental interagency testing program, you know, we - you would have your own testing that you do, but it'd also be double checked if amenable at the NCI. So we'd have that data as well, to support the application. So we have not required for such a task that the samples be US-based. We'd like to see US-based.

For point of care, I'll just say because I brought it up, it is important that the setting for point of care testing, you know, mimic the US. And it's ideal if the point of care studies can be in the US because how, you know, point of care testing is done in the US can be substantially different from other countries. And we certainly see, you know, point of care studies done in central laboratories with trained workers.

So that's obviously - even though it might be a device that's amenable to point of care that's not what we're looking at. We're looking at can an untrained healthcare worker who is not a laboratorian, perform the test and get accurate results? But anyway, back to your question. Yes, we have no requirement for US samples and US testing although it's ideal.

(Elaine Allen): Will there be any benefit to us tracking regions of those samples?

Dr. Timothy Stenzel: That sort of thing may only come up if we see funny results and we're trying to figure out, you know, what's going on. So it's best to capture as much relevant information as you can on these samples, because we often want to know how is it - where they're collected; when were they collected; and how were they stored if they're banked? All those questions are really

important. And then all the relevant important information, you know, is important as well.

But, you know, I anticipate with the variants progressing, our evaluation of all the tests, is going to be more challenged. And the validation of the test might be challenged as well by variant. So - and so…

(Elaine Allen): Absolutely. Yes.

Dr. Timothy Stenzel: …our experiences early in the pandemic may be different for serology and other tests, than they are currently or in the future. So it's just unfortunately, something that we're all going to really need to stay entirely on top of.

(Elaine Allen): Yes. We're keeping our ear to the ground on that one as well. So thank you very much. That was very helpful. I appreciate it.

Dr. Timothy Stenzel: You're welcome.

Coordinator: Our next question comes from (Misha Lee).

(Misha Lee): Yes, hi. Thank you for taking my question. Following up on the topic of mutation testing, I know it was indicated on the last town hall that FDA is proactively reaching out to already authorized molecular developers to conduct additional testing. My question is for manufacturers that will be submitting their new like point of care nuclear protein based antigen EUA, is there any additional variant testing required as part of the initial EUA submission?

Dr. Timothy Stenzel: So let me, you know, ask the question of you, because I am going to reach out to all of the EUA authorized antigen test developers. You know, can you

use say even activated antigen or virus and/or a radiated virus from BEI, because this - if we can - if antigen tests can - those antigen tests that can use this and of course a lot of this is going to be comparing to the original strain that was deposited at BEI and we typically think of that as anything comparing to that.

But if an antigen test is amenable for use of inactivated virus that makes all of our lives a lot easier as far as testing reactivity and inclusivity. And it's my understanding that the UK variants have been deposited BEI and I'm just going to be double checking with them that they are planning to inactivate that.

So we haven't figured that all out yet. We just know that at least for key variants we're going to start wanting to know, you know, if there's any loss of sensitivity with those variants. And we're trying to figure out the very best way to do this and using live virus in a lab is not ideal. But if inactivated virus can be used then potentially panels can be distributed to developers and to tests that are already on the market.

(Misha Lee): Thank you very much.

Dr. Timothy Stenzel: But stay tuned is the bottom line. But obviously, the mutation - variants of interest right now to keep up with health importance, are the UK variant, the South African variant and now what's called the Brazilian variant. Okay?

(Misha Lee): Okay. So in terms of testing the type of variants, are those the only two that we should be testing or what is the best way to keep current on the type of variant?

Dr. Timothy Stenzel: So we are working through this process. So in all likelihood we'll be updating template; in all likelihood we'll be updating letters of authorization of these going forward; in how best to do this. So, and we're just at the beginning stages of thinking through this. It would be ideal if we can be using in silico analysis to some degree. We use it of course for molecular.

But if we could start using it for antigen and serology tests. So we are going to start beginning to ask developers how they think they can monitor variants for variants of concern. And obviously I've mentioned three variants - South African, UK and Brazilian. But there could be - and those are important because they appear to be more infectious and could have potential impact on the vaccine efficacy.

So - but there could be one or more variants out there that in accumulation, could start to depress the sensitivity of assays. There's even some cases we're thinking in serology examples, typically for neutralizing antibodies, where there could potentially be false positives. Right? So you have neutralizing antibodies to, you know, a prior infection but not to, you know, some of the variants.

So all I can say right now is this is one of our top priorities if not the top priority right now, for our office and our center and the ability of the agency as well, to try to figure out how to best do this. So certainly we have been having lots of conversations.

So in all likelihood as I said, we're going to be asking - doing a template update, asking developers, you know, what are their thoughts for how they can monitor for impact of variants and work with us essentially, to figure this out. And whether modeling for antigen and serology tests can be used, is too

early for me to say how useful that is to figure out if a variant could have an impact.

And then if there is a potential impact, for molecular tests already we have been asking the last developers to do blood testing to make sure that the variants don't mess with the sensitivity of the assay. And we want to keep that kind of wet testing to a minimum if possible, because there are just so many variants obviously.

(Misha Lee): Okay. Thank you very much. Sorry. You had mentioned that there's - that you guys are working on updating the template. So before that update do you suggest that we reach out to the EUA, you know, just to obtain specific guidance on variant testing?

Dr. Timothy Stenzel: You can, but I don't think we're ready to give recommendations right now. We're focused on, you know, we're doing it for molecular. And all molecular developers do this in the process of submitting their application. They survey the landscape. I just - since we don't have a solution that's really workable yet, for antigen and serology, I don't want to be making recommendations about that.

But other than to - we want to know what your thoughts are about these. And as we develop our knowledge base and information base and as we discover ways to do this better, we may update those recommendations. But certainly, if you want to bring it up I'm not holding you back. I mean I think it's a sign of a good developer that brings up these issues.

I just don't want to hold back authorization until we can figure out how to do this right. We are likely to, in addition to template asking, for what your thoughts are on how to monitor the impacted variants we are probably going

to put that into a commitment for post-market monitoring. And if you discover something, to contact us and we'll figure out the next steps.

And the other thing is - these are just thoughts, nothing's settled, nothing's determined yet. But I think it is an important topic and it doesn't hurt to bring this topic up as we try to work through it.

(Misha Lee): Thank you very much Dr. Stenzel.

Coordinator: Our next question comes from (Stacy Houseman).

(Stacy Houseman): Hi Dr. Stenzel. Thank you for taking my call. I'm - I work for a CRO and I'm currently working with a client who is working on a rapid antigen study. And they plan to have their own proprietary transport media. They've seen some lower sensitivity in the universal transport media, so they plan to use this proprietary media.

And according to the template, they plan to do retrospective samples for the method comparison. But according to the template, there is a requirement or recommendation that because of erroneous results seen in transport media, that there is the prospective enrollment of it says 30 positives, five of those needed for the EUA submission and then the other 25 can be done post-authorization as a condition.

So my question is I heard you earlier with another call, saying that there were also negative samples, fresh samples required for that. And so I wanted to verify that that is correct. And then also if they're using their own proprietary transport media is it still necessary to demonstrate the low risk of erroneous results using transport media versus a dry swab?

Dr. Timothy Stenzel: So if it's a new transport media device, one we haven't authorized before, we're going to want to know that it in and of itself, doesn't result in inaccurate results, and that using it in transport preserves the target. Then - and you know what the temperature profile and time profile are in experiments and basic transport experiments.

I'm not sure if that addressed your question. I'm not sure that I fully understood your question.

(Stacy Houseman): Well if there - okay, so in the template right now, if one uses - if retrospective samples are used for the comparison study to RTPCR method the template suggests that because of erroneous results that have been seen in samples that were stored in transport media, there is a prospective study that is needed - 30 positive samples, five of which are needed in order for the EUA submission. And then the other remaining samples can be enrolled after. Is that correct?

Dr. Timothy Stenzel: That's the recommendations for point of care fresh samples versus using banked samples. So you can do a complete study with banked samples but then fresh samples - we want to see some fresh samples because banked samples, especially frozen, can potentially alter the performance. Sometimes it increased performance of a device to do a freeze thaw.

So are you talking about the comparator transport or are you talking about your candidate device transport media?

(Stacy Houseman): Well the retrospective samples will be in UTM and…

Dr. Timothy Stenzel: Okay.

(Stacy Houseman): …so it'll - that'll be used for the comparator method. And the candidate method. But then the prospective…

Dr. Timothy Stenzel: Okay.

(Stacy Houseman): …study will be done using their proprietary media.

Dr. Timothy Stenzel: Oh, okay. Yes. So that presents a challenge that I want you to discuss with the - with your reviewer or to the Templates email address. Because you're using a different media for a validation and a media could have an impact. So the reason to allow retrospective samples in the testing, is to speed access to the market of an innovative test.

And it really needs to be - everything else sort of needs to be the same. You know, so if you have…

(Stacy Houseman): Okay.

Dr. Timothy Stenzel: You know, if you - if your test is dry swab then we want to see - you can have collection of frozen banked dry swabs and the fresh study needs to be in dry swabs. But if it's in transport media it needs to be in the same transport media, so that we can use the data from the banked samples to presume performance of the test with only a handful of fresh samples to prove that fresh samples work pre-market. Okay?

(Stacy Houseman): Okay. So if I use retrospective samples in UTMs then they'll still need to do a full fresh prospective enrollment study with their own transport media, in order to submit this?

Dr. Timothy Stenzel: Yes. So it's important to validate it with the transport media you're going to use for the test.

(Stacy Houseman): Okay.

Dr. Timothy Stenzel: And so if you are going to - so we certainly can give, you know, a moderate or high complex authorization based on banked samples and use of UTM for transport media. But you've got a new media and we don't know how it performs at all and we don't know if it's equivalent to UTM or not. And so we do need to look at the data for the new media.

(Stacy Houseman): Okay. Okay. All right. Thank you so much.

Coordinator: Our next question comes from (Scarlet Shaw).

(Scarlet Shaw): Hi. Thank you so much for taking my question. I have a question about asymptomatic screening as it relates to antigen tests. The template indicates that you should test in the subject without symptoms and without other reason to suspect infection. So as part of this without other reasons to suspect infection, we're sort of wondering what timeframe would be considered appropriate to say no symptoms plus no known contact with someone who is positive.

So would 21 days be an acceptable time limit or should we consider a greater time limit for no contact with someone that's infected?

Dr. Timothy Stenzel: So the goal of this is not to enrich with people who might be pre-symptomatic, right, and if they were exposed recently. That would, you know, potentially, you know, give the candidate test an advantage and not truly test what we're looking for is an asymptomatic population. Formerly we

have defined asymptomatic as at the time of testing they have no symptoms and they don't have any prior test results, positive test results or symptoms.

I would think - I'm not sure if we have a specific day in mind here. But it would probably need to be in at least the 14 to 21 days. You know, I think that's something that I can't give a formal answer on because I don't have a prepared response today. So, you know, it's probably best to check with the Templates email in our email box - or if you already have the reviewer, with the reviewer for what the update of unknown symptoms should be, prior to testing, or no exposure prior to testing.

(Scarlet Shaw): Okay. Thank you so much.

Coordinator: Our next question comes from (Jackie).

(Jackie): Hi. Hello?

Dr. Timothy Stenzel: Hello.

(Jackie): Hi. Oh, hi Dr. Stenzel. I have a question about getting vaccinated to include the vaccinated population in serology or a neutralizing antibody test. And my question in particular, is on the clinical study design. I am interested in understanding FDA's thinking on the sample size and also the acceptance criteria, because there's not that much that we know about the vaccinated population at the moment.

So a lot of the information we will gather will be observational. Yes, like it would be an observation. So we're trying to get FDA's thinking on how to best design this clinical study.

Dr. Timothy Stenzel: Can I ask a clarifying question? Sorry. I missed it probably. You're wanting to know if you can include vaccinated folks in your test or are you looking at trying to predict if there's a good vaccine response or immune response?

(Jackie): Yes. Yes. We are trying - we think we can - yes, we are trying to look for if a patient gets a good vaccine response.

Dr. Timothy Stenzel: So that is something that we've not provided template recommendations for. It's, you know, and it's something that, you know, we would dialog with CBER who reviews the vaccine. To date they haven't been interested in, you know, sort of companion diagnostics here at the moment. But I always defer to them and our thinking always can change quickly.

The - I mean obviously there could be some benefit here. But what would you say - and we'd basically say after vaccination and we - well, you've got antibodies for SARS-CoV-2 right? It, you know, going the extra mile, you know, that says well, what does that mean, you know, is a little bit of the challenge. Right?

So the bottom line is we don't have current recommendations for such a study. But we are letting people know that if they want to do such a study that they can propose a study design and we would review it a the moment. And of course we would not just review it in our center, the device center, but also in the biologic center.

(Jackie): Yes. We have a proposal but we wanted to mature the sufficient sample size and the challenge is that right now we don't know how to set the acceptance criteria because it's still an observational study. So we would just track patients, or not patients but individuals who have received a vaccine, over a

period of different days, like a different time point every week, for a certain amount of time.

Dr. Timothy Stenzel: Yes. I would again, just recommend that you put your best thoughts into a proposal and then ask the questions that are unanswered. And I don't know if you've already submitted it or not. If you have submitted it did you get responses already for those?

(Jackie): No. We really wanted to do a good job before we sent it over. So we plan to submit it soon, as a pre-EUA format. So thank you.

Dr. Timothy Stenzel: Yes. Oftentimes when we have new developers coming with new ideas, shall we say, we like to really explore those ideas with the first several developers, so that…

(Jackie): Okay.

Dr. Timothy Stenzel: …we can then formulate a potential recommendation that makes sense. Okay? We don't…

(Jackie): Okay.

Dr. Timothy Stenzel: And so I think that dialog with our staff, could be very beneficial to you and certainly would evolve our thinking into the point where we might be able to start formulating some recommendations.

(Jackie): Okay. We would really appreciate the dialog. Can we send it in an Excel format or oh, we probably should put it in writing. Right?

Dr. Timothy Stenzel: Yes. You can attach an Excel spreadsheet but, you know, we want it to - it's best to be in written form.

(Jackie): Okay. Thank you so much, Dr. Stenzel. Thank you.

Coordinator: And that will be our last question. I would now like to turn the conference 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 transcript will be made available on the CDRH Learn Web page at www.FDA.gov/Training/CDRHLearn, by Friday, February 5. If you have additional questions about today's presentation, please email CDRH-EUA-Templates@FDA.HHS.gov.

As we continue to host these virtual town halls we would appreciate your feedback. Following the conclusion of today's town hall, 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. Again, thank you for participating. This concludes today's virtual town hall.

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