

**Virtual Town Hall #85  
May 18, 2022**

**Moderator: CDR Kimberly Piermatteo**

**CDR Kimberly Piermatteo:** Hello and welcome everyone, to Virtual IVD Town Hall #85 for SARS-CoV-2 test developers, in which we'll discuss and answer your questions about diagnostic tests in response to COVID-19. Thanks for joining us today. This is Commander Kim Piermatteo of the United States Public Health Service, and I am the Education Program Administrator within the Division of Industry and Consumer Education in CDRH's Office of Communication and Education. And I'll be your moderator for today's Town Hall.

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

The May 4th IVD Town Hall recording and transcript have been posted. The next scheduled IVD Town Hall will be on Wednesday, June 1st, 2022 from 12:05 to 1:00 PM Eastern time.

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

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

I'd now like to welcome Toby, who will provide today's opening remarks. Toby, the floor is yours.

**Toby Lowe:** Thanks, Kim. And thanks, everyone, as usual, for joining us for the Town Hall. A couple of announcements about recent actions. On the 10th of this month, so just over a week ago, we issued a new safety communication about a particular antigen test from Skippack Medical Lab, the Skippack Medical Lab SARS-CoV-2 Antigen Rapid Test, distributed by SML Distribution. And they recalled that test because it is not authorized, cleared or approved by FDA. And we also issued that safety communication and the class one recall notice for that test.

And then just earlier this week, on Monday, we authorized the LabCorp Seasonal Respiratory Virus RT-PCR DTC test. So this is a direct-to-consumer home collection test. And it is the first test that is available without a prescription that also detects flu and RSV. So that's an exciting advancement there.

And I believe those are both showing on the slide right now. And they'll be posted with the slides if you haven't seen those links yet. So that's it for the announcements. So we can go into the prepared questions.

**CDR Kimberly Piermatteo:** OK. Thank you, Toby. We'll now answer your previously emailed questions about COVID test development and validation. As mentioned before, please note we do receive some questions that are too detailed or test case specific that we will not address during today's Town Hall. For those questions, we will try to send a response in writing within a few days. If you have submitted a

question and do not hear it addressed today, please look for a written response. If you do not receive a response within a few days, please feel free to reach back out to the [CDRH-EUA-Templates@fda.hhs.gov](mailto:CDRH-EUA-Templates@fda.hhs.gov) mailbox for an update.

Alright, Toby. Our first question is, is FDA prioritizing review of OTC tests versus prescription home use rapid diagnostic COVID test kits?

**Toby Lowe:** So FDA's current thinking on prioritization of In Vitro Diagnostic EUA requests is explained in the FDA guidance document Policy for COVID-19 Tests During the Public Health Emergency. That is the version that was issued on November 15th of 2021. And as discussed in section 4A of that guidance document, the priorities do not specify prescription status, but they do focus on tests that will significantly increase testing capacity and accessibility. Generally, the ability for consumers to purchase or otherwise acquire, since there are free distribution programs, home tests without a prescription typically would increase access to testing more than a test that requires a prescription.

**CDR Kimberly Piermatteo:** Thank you, Toby. Our next question is, what is the average timeline for manufacturers who submit EUA or COVID-only or COVID-flu combo tests?

**Toby Lowe:** So we do have an FAQ that addresses this a little bit. And that FAQ is posted on our website. It's titled "I submitted a pre-EUA or EUA request for a COVID-19 test. How long will the review take?" And in that FAQ, we are clear that we try to review pre-EUA and EUA requests as quickly as we can. And we do communicate with each sponsor regarding their pre-EUA or EUA request as soon as possible. The timeline for a specific submission, however, is dependent on many different factors, including the priority of that submission, and the quality of the submission and the data provided.

**CDR Kimberly Piermatteo:** Great. Thanks, Toby. Our next question is, what clinical validation strategies would FDA recommend to support authorization of a multi-analyte test? What portion of the 50 flu A and 30 flu B samples must be prospectively collected fresh samples, as opposed to retrospective banked samples?

**Toby Lowe:** So if your test has a claim for use with a transport media, then we would recommend evaluating the clinical performance with a prospective clinical study conducted for at least two weeks. And after the two-week duration, if you have not collected the recommended number of positive specimens, then a clinical validation study using retrospective samples may be conducted at one of your testing sites.

In that case, you should test archived positive and negative clinical samples. And we do know that the reduced prevalence of influenza last season may make archived specimens difficult to obtain, but we do still recommend testing archived samples to support authorization.

We will accept 100% retrospective positive samples for flu if the two weeks of prospective testing results in none or less than the recommended number of positives. And then there would likely be a condition of authorization to complete a post-authorization clinical study. And that can be discussed during the review of your EUA request.

We generally would recommend that you refer to the template that's available on our website for additional information. And then if your test has a claim for use with a direct specimen-- and this is for antigen or molecular, where the swab is placed directly into a proprietary buffer after specimen

collection, instead of using a transport media-- then we would recommend discussing potential use of banked samples with us prior to initiating your study, since there are some additional challenges in those cases.

**CDR Kimberly Piermatteo:** OK. Thank you, Toby. Our next question is, will FDA still be accepting EUA requests in July?

**Toby Lowe:** The EUA pathway is currently still available, but we're not able to speculate or predict when it will be ending or when the priorities may shift. We are encouraging developers to start moving towards full marketing submissions. So you may want to consider whether your data may support full marketing authorization.

And we also recommend that you refer to the recently published FAQ regarding the difference between the public health emergency declaration and the EUA declaration. And that FAQ is titled, "What will happen with tests offered under EUA if the public health emergency expires and is not renewed?"

**CDR Kimberly Piermatteo:** OK. Our last previously submitted question for today is, can moderate to high-complexity labs that are not CLIA-certified and who do not generate or report patient results be used to perform a clinical study to support an EUA, either pre-market or post-market?

**Toby Lowe:** From an FDA perspective, we do not have an issue with a clinical study being performed in a non-CLIA-certified lab, provided there is appropriate IRB oversight and the results are not returned to the patient or provider, and that the laboratory is able to perform the testing according to an appropriate study protocol. And this is true for moderate and high-complexity tests. This is not appropriate for waived tests.

**CDR Kimberly Piermatteo:** Great. Thank you, Toby.

**Toby Lowe:** Or tests seeking waived status.

**CDR Kimberly Piermatteo:** OK. Thanks, Toby.

**Toby Lowe:** Sorry about that.

**CDR Kimberly Piermatteo:** No worries. Alright, Tim, we're going to go ahead and turn it over to you for some additional remarks today.

**Timothy Stenzel:** Alright, thank you, Kim and Toby. Yeah, so I note that, yesterday, it was estimated in the U.S. that there was around 700,000 U.S. COVID positive test results. The vast majority of those are likely over-the-counter home test results, but the official numbers may underrepresent how many COVID cases are still occurring on a daily basis in the U.S. So unfortunately, in the U.S., for SARS-CoV-2 at least, there are, unfortunately, plenty of positive patients for test validation work.

Turning to the panel tests, particularly flu, we get a lot of questions about what to do about flu, especially flu B. I will note the latest weekly report from the CDC reports that the percent of flu positives within influenza-like illnesses is at 8.6%. So among those who were thought to potentially have flu in the United States, there is a significant number that are actually flu positive. In addition, in the last week,

there have been more than 3,000 hospitalizations for flu. So it is, unfortunately, a significant problem in the U.S.

The challenge for test developers, at least in the U.S., is that 99.2% of the flu positives that are circulating now are flu A. So flu B, at the moment, is only 0.8% of the flu positives. So where it may be feasible to get flu A in the U.S. now with a well-designed, well-coordinated and well-stationed study, even where there is flu, getting sufficient prospective fresh flu B positive is going to be challenging.

I think if there are areas of the world where flu B is circulating, I think the FDA is going to be open to being able to go there, because there are some technologies, particularly direct detection technologies, that don't go into a VTM, which Toby mentioned earlier. And VTM for rapid antigen tests is problematic when it includes, at least for SARS, because we've seen so many challenges with VTM, and nearly all, if not all, of the antigen tests have moved away from the use of VTM.

There are potential use of saline, but by and large, it is a direct swab. So getting banked direct swabs samples for evaluation of a flu A/B test is going to be challenging. And so prospective collection is still one option. So we're going to display some flexibility on where in the world you get the flu A/Bs.

Also, Toby hit on this, as well, but really want to emphasize the importance of seeking full authorization as soon as possible for any developers who do want to stay in the market. So I encourage you to get started, if you haven't already. Q-Subs for full conversions of molecular antigen and serology tests are being accepted. So reach out, and we'll give you some recommendations on those validations. And with that, we can, Kim, go back to you and open it up for live questions. Thank you.

**CDR Kimberly Piermatteo:** Great. Thank you, Tim. Alright, we will now take your live questions. So to ask a live question, please select the Raise Hand icon at the bottom of your screen. When you are called on, please follow the prompt in Zoom to unmute yourself, then identify yourself and ask your question. Please remember to limit yourself to asking one question only. If you have an additional question, you may raise your hand again to get back into the queue, and I will call on you if time permits. And lastly, please remember we are not able to discuss device or specific submissions under review.

Alright, our first live question is coming from Wendy. Wendy, I am going to unmute your line. Please unmute yourself and ask your question.

**Wendy HMC:** Can you hear me?

**CDR Kimberly Piermatteo:** Yes, I can.

**Wendy HMC:** OK. Hi. Good afternoon. I'm from Hopkins MedTech Compliance. I have a question regarding applying 510(k). We are helping a molecular test developer to conduct their clinical study. It's for a lab testing. So I'm wondering, I want to find out how many positive case if we need to apply for the 510(k)?

**Timothy Stenzel:** So that's a perfect example of submitting a Q-Sub. You can also, for molecular tests, you can look to the special controls that have been published and the decision summary that have already been made public for the first two molecular full authorizations for SARS-CoV-2. They also included panels. So for anybody that wants to go through the 510(k) submission for that type of test,

those are really good resources. And what you don't get there and what's not clear there, then put into a question or two or more in the Q-Sub. And there's no charge for the Q-Sub. That's a free submission.

**Wendy HMC:** OK, so sorry, I'm a little bit lost. So where I can find a guidance document?

**Timothy Stenzel:** Yeah, so might be able to list that next time, where you can find these documents. It's probably a good thing for us to do. But there is a Q-Submission, Pre-Submission guidance. So if you were to simply Google FDA Q-Submission or Pre-Submission, I believe it's CDRH, that then usually will come up pretty quickly.

**Wendy HMC:** OK. Appreciate that. Thank you so much.

**Timothy Stenzel:** Mhm.

**CDR Kimberly Piermatteo:** Thank you, Wendy. Thank you, Tim. Alright, our next question is coming from Annie. Annie, I'm going to unmute your line. Please unmute yourself and ask your question.

**Annie Wright:** Hello. Thank you so much for taking my question. I had a question for OTC testing regarding the randomization testing, because we've been talking to some CROs, and they basically say that they've been told by FDA not to randomize because it was more important to keep the test blinded, in the sense that they wanted to do the RT-PCR testing first, and then the device, the investigational device second. Is that--

[INTERPOSING VOICES]

**Annie Wright:** Over the counter, yeah, because our plan was to--

**Timothy Stenzel:** --molecular--

**Annie Wright:** --have them do alternating, but depending on birthdays. Birth year, sorry, birth year. And then so they would alternate, so there would be randomization. But they said that was not necessary, so.

**Timothy Stenzel:** Well, Annie, let me--

[INTERPOSING VOICES]

**Timothy Stenzel:** --so this is-- go ahead.

**Annie Wright:** Oh, sorry, go ahead.

**Timothy Stenzel:** I was going to ask, this is over the counter molecular or over the counter antigen?

**Annie Wright:** Over the counter antigen, sorry. Over the counter antigen.

**Timothy Stenzel:** OK. OK. Yeah, so the response to this can depend. But based on what you're telling me, the purpose for collecting the comparator results, which also potentially could be the test of record,

but that's where it can be tricky sometimes with IRBs, but if you're doing a comparator test, the reason to take that second in all cases is we're trying not to train the user on how to collect a swab.

So if they get administered a swab right before they take a swab of their own, that could provide them training that users out at home won't have that training. They won't have somebody swabbing their nose right before they do a self-swab. So we want to look at an unbiased picture of the OTC users.

So you can put in, say, a 15-minute washout period. So some developers have had a participant perform the candidate device test. That usually takes-- it could take 15 to 20 minutes, right? And then when they finish, you can have a health care worker swab their anterior nares, if that's the competitor swab, and then they're done. So if you just use the time of testing, that provides, we believe, a sufficient washout period between the first swabbing of the nose to the second swabbing of the nose. So it should not impact the comparator test result.

**Annie Wright:** Yeah, so we shouldn't do any randomization. It's not expected by FDA.

**Timothy Stenzel:** No.

**Annie Wright:** OK.

**Timothy Stenzel:** Well, it would introduce bias into the home testing, where the user would be trained, and sometimes, to some degree, on how to collect their own swab.

**Annie Wright:** OK, so not worry about it. Just keep it the--

[INTERPOSING VOICES]

**Timothy Stenzel:** It's not a matter of worrying.

**Annie Wright:** I mean--

**Timothy Stenzel:** We do not recommend-- we do not recommend--

**Annie Wright:** Oh, OK, OK.

**Timothy Stenzel:** --you randomize in this situation.

**Annie Wright:** Correct, OK.

**Timothy Stenzel:** And if there's anything comes up that's a challenge, you can reach out, such as IRB rules or something like that.

**Annie Wright:** OK. And then in terms of the asymptomatic, or can we submit with just symptomatic claims for the first phase, and then proceed with asymptomatic mid-submission, or during the submission we continue our study, and then have it, like, ready for post-submission?

[INTERPOSING VOICES]

**Timothy Stenzel:** Yeah, so we can disconnect those. And there's been some subtle changes in this guidance recently. So there's been some changes to the guidance recently. And I think I'd like to turn that over to Toby or to Kris to go ahead and respond.

**Kristian Roth:** Toby, I don't know if you have anything, but I think that adding additional claims, and especially for asymptomatic folks, or screening claims or anything of that nature, I think, is something we probably want to interact with you in the context of your test. So it'd be better to understand where you are in your validation and all of those details. So I would suggest sending an email in, and so we can have a more detailed conversation about what exactly you all want to do.

**Annie Wright:** Oh, OK, because the CRO suggestion is to basically do the first phase or whatever, and do it as just purely symptomatic. And then we can submit the EUA with that data.

**Kristian Roth:** Yeah, this is all kind of regulatory strategy stuff that probably is better discussed in the context of your response, or of your specific test.

**Annie Wright:** OK. So you recommend that we just send in an email, or do we have to do a Pre-Sub?

**Kristian Roth:** If it's a short question--

**Annie Wright:** It's a short question, yeah.

**Kristian Roth:** --then email is perfectly fine. And you can help us to understand kind of where you're at. If it's kind of more involved and we need to look at the study protocol, then a pre-EUA is likely more appropriate.

**Annie Wright:** OK. Alright, thank you so much.

**CDR Kimberly Piermatteo:** OK. Thanks, Annie. We're going to move on to our next question. Our next question is coming from ArionBio. ArionBio, I have unmuted your line. Please unmute yourself and ask your question.

**ArionBio:** Yes, can you hear me?

**CDR Kimberly Piermatteo:** Yes, we can.

**ArionBio:** Yes. Yeah, this is [INAUDIBLE] from ArionBio. So my question is about the home use antigen test, the reporting, the result reporting mechanism. So for EUA award the full authorization, what's the difference of this request for the manufacturer to provide a result reporting mechanism? And even we provide like a cell phone app, that the user may still not report their results through the app. So what should we do? What's the request from FDA? Thank you.

**Timothy Stenzel:** Yeah. So yeah, let me go over what's recommended or encouraged for EUA. So for an EUA authorization, it is not a requirement for a decision to have a reporting feature. If you don't have a reporting feature that we view at the time of authorization, then we do have a post-market commitment for the test developer to come up with a method for users to be able to report their results.

Usually, reporting results in this situation is voluntary. And so the users have the option to opt out of reporting, or they can choose not to report. However, it is encouraged. And it is encouraged, obviously, for them to report results to their health care worker, even if it's an over-the-counter test. So we totally understand that consumers, especially if it's a manual entry versus an automated entry of results, that the consumers may or may not do that.

So we can't hold the test developers responsible for results not being reported because it is a voluntary aspect by users. As far as recommendations for full authorization, I think that's best handled, again, through a Pre-Sub/Q-Sub. But we anticipate that those that get an EUA and then develop a reporting feature will carry that on through their full authorization submission.

**ArionBio:** Yeah, so what I heard is that the 510(k), or the full authorization, mandatory result reporting mechanism that the app has to have a function to force the user to report the result. Otherwise, it won't pass the 510(k). Is that true? Or in that case, I wonder all of these current home use rapid antigen tests will not meet that request, right?

Maybe only those automatic detection, like Ellume kind of product, that they can-- because they read the results through an instrument, and then they can be reported automatically. But if the results being inspect by visual check, then it's still up to the user to report, right? So do you know anything about this request?

**Timothy Stenzel:** So again, that was requested of you by the FDA?

**ArionBio:** No, no, no, I just heard a rumor saying these kind of--

[INTERPOSING VOICES]

**Timothy Stenzel:** We don't deal in rumors — we deal in --

**ArionBio:** Yeah, I'm sorry for that.

**Timothy Stenzel:** --communication and facts. So again, the process for this for full authorization, let's discuss that under a Q-Sub/Pre-Sub for your conversion.

**ArionBio:** I see. OK.

**Timothy Stenzel:** OK.

**ArionBio:** Thank you.

**CDR Kimberly Piermatteo:** Thank you, Tim. Alright, our next question is coming from Sue. Sue, I have unmuted your line. Please unmute yourself and ask your question.

**Sue Hart:** Hi. This is Sue Hart from Henix Health. I remember that recently an email came out notifying that CDRH has split into two new organizations. And that email did not include the address for sending in documents to the Doc Control Center if your submission for your POC or OTC antigen test documentation set is too large to be emailed to templates. Can you provide the address, and how you address your cover letter in this case?



**Timothy Stenzel:** So the office that I've led since joining the FDA in 2018 has spun off a new office.

**Sue Hart:** Right.

**Timothy Stenzel:** The new office is the Office of Radiological Health. The processes and procedures for IVDs is unchanged, to my knowledge. Toby, do you have any update?

**Toby Lowe:** Yeah, that's correct. I think we announced this on the Town Hall last time. There is no change for IVDs. So if you have the Document Control Center mailing address that you've used previously, it has not changed. It's also on the webpage for the eCopy Program for Medical Device Submissions. And that is the Document Control Center for all submissions to CDRH. It doesn't change, depending on which office.

**Sue Hart:** OK. Thank you very much.

**CDR Kimberly Piermatteo:** OK. Thank you, Sue. Our next question is coming from Homer. Homer, I have unmuted your line. Please unmute yourself and ask your question.

**Homer Wu:** Hi. Thanks for taking my call. I'm from Hopkins MedTech Compliance. We submit a pre-EUA, I believe on April 9th. And we get a pre-EUA number, but since then, we haven't heard anything. The pre-EUA is for COVID-19, flu A and flu B combo OTC test. So—

**Timothy Stenzel:** OK. Yeah, sorry about that delay. Toby and I can look into that. So if you email the template email inbox and ask for your email question to be forwarded to Tim and Toby, we will look into that and resolve that issue for you.

**Homer Wu:** OK. Thank you.

**CDR Kimberly Piermatteo:** OK. Thanks, Tim.

[INTERPOSING VOICES]

**CDR Kimberly Piermatteo:** OK. Alright, our next question is coming from Kay. Kay, I have unmuted your line. Please unmute yourself and ask your question.

**Kay Taylor:** Yeah, hi. This is Kay Taylor from BD. And Tim, my question is around a direct swab antigen test for OTC for COVID, flu A and flu B. And I'm just building a little bit on the earlier guidance that FDA was open to samples that were collected outside of the U.S., especially with the flu B, and possibly the flu A.

My question is, is there-- or what is the current thinking on the number of acceptables? So for an EUA, I understand it's 50 positives flu A, and I think 30 flu Bs. Does FDA have any guidance or any current thinking on how many of those could come from the southern hemisphere, since their flu season will be in front of our upcoming one this fall?

**Timothy Stenzel:** Yeah, so 50 and 30 for flu A and B is correct. And we obviously would prefer direct fresh samples. And anywhere in the world is fine. We would want you to do, for an OTC test, we would

want you to do a study in the U.S. to get any positives you can here, including, obviously, the COVID positive. And you should accumulate enough negatives for the whole study, then, under that situation.

But we do want, we do recommend that you have U.S.-based experience. But to get the actual numbers for flu A and B, and if you prefer to go outside the U.S. rather than try to find banked samples that might work, which is going to be really challenging, then please go ahead. It's probably good to just let the FDA know what your plans are there so that we can give you any feedback if there's any issues with your plans.

**Kay Taylor:** Alright. Thank you, Tim.

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

**Wenli Zhou:** Alright, thank you very much. This is Wenli Zhou from XYZ Laboratory. And I have a question about the banked sample, using bank samples for flu A/B OTC and rapid antigen test. Just as Tim and Toby talked earlier, that some of those VTM samples, or VTM may not be good when you're using the samples in the direct test.

My question is, if we know that there are some VTM or some buffer that are actually good, that don't affect the direct test, it's just there's dilution factors because the swab is in the medium. So if we can actually validate that or confirm that the medium is fine, there's no inhibitory effect, then we can use it, right? So we can use those banked VTM samples for those other vials.

[INTERPOSING VOICES]

**Timothy Stenzel:** So there's two challenges with that. Of course, you are highlighted one, that there's a dilution. And so your performance may be lower for both SARS-CoV-2 and flu A and B when you dilute the sample before going on your device. And there's challenges in getting home users to do that kind of testing because it changes the workflow for your assay. Plus, I would recommend that you check the buffer with the FDA first, because we really have seen widespread issues with VTM.

And it appears to be, in some cases, lot specific. You might have some lots that perform just fine, and other lots that don't. And the actual root cause of those false positives with VTM is not yet well-understood enough to know how it could be prevented. We're looking at established FDA-regulated VTMs and the challenges that we've seen with them.

**Wenli Zhou:** So in this case, what's the best approach? It's check with the FDA, or [INAUDIBLE]

**Timothy Stenzel:** Yeah, I would submit a pre-EUA with your plans, along with whatever buffer you're going—

[INTERPOSING VOICES]

**Timothy Stenzel:** --how you're going to run your study, how you're going to—you know it will be a different workflow for users if they self-collect and then go through a VTM. We'll want to look at what's in the buffer and is it safe for home use. Those are all those questions that are more challenging when you can't get a direct swab sample in high enough numbers right now.

**Wenli Zhou:** Yeah, so this particular question, yeah, so basically it's more like use those frozen sample to actually test the performance of the device itself. It's not ready for like home tests that people put there, swabbing, so it's more like to check the difference between using those banked sample versus using a direct swab sample.

**Timothy Stenzel:** So for over-the-counter tests, we do want to know how users are able to use that. So that's one of the challenges that need to be worked out with the FDA, rather than do something and it not be sufficient for authorization.

**Wenli Zhou:** OK. Alright.

**Timothy Stenzel:** And if you're using frozen banked samples in antigen tests, that introduces another important variable. We have seen performance change on pre-stock. So we'll need to see a pre-stock comparison study showing that there's no change in performance.

**Wenli Zhou:** OK. Alright. OK, great. Thank you very much. We'll just work with the FDA, and once we have those Pre-Sub and assigned lead reviewer, OK, thank you.

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

**Andy Wang:** Hi. This is Andy Wang from BIA. Thanks for taking my question. This might be a little bit technical question related to PCR COVID tests. Different agencies, such as CDC and WHO, have different recommendations for targeting genes. And for WHO, they recommend e-Gene for first-line screening, and confirm positive case with RDRP Gene. In the market, there are so many different combinations, different targets. What is the FDA's viewpoint on this, and what's the recommendation to any FDA filing related to target genes and RDRP or et cetera?

**Timothy Stenzel:** For molecular assays, we do recommend two or more targets. And we also recommend highly conserved regions. So in general, the e-Gene is going to be sufficient for those purposes. We do ask you do inclusion in silico analysis to make sure that the primers and probes you select will properly deal with the variants currently in circulation. We'd want to know, even for past variants, just to know how they might be affected, because it just kind of tests the robustness of your design.

So it sounds like that, if there's other territories that have specific recommendations on how you do the testing, they can be incorporated into a molecular test for U.S. authorization. So the FDA is not being directive in which genes you target. Kris, anything else to add on my comments?

**Kristian Roth:** No. I think choosing a gene target is something that's specific to your technology, and you also should keep in mind how the sequence is conserved. I think you mentioned e-Gene. We've seen a lot of conservation in that particular gene as the variants kind of come and go. Certainly the spike gene, there's quite a bit more mutation that you're seeing. So I think that's probably something to consider, as well.

**Andy Wang:** Just a quick follow-up. You mentioned that you recommend two or more genes?

**Timothy Stenzel:** Yeah. That's really recommended. There are some technologies that are only capable of doing one, but we have seen more potential issues with single-target assays because of all the mutations. And it has caused those developers some challenges, and some of them have had to redesign their assay to deal with the variation.

**Andy Wang:** Thank you.

**CDR Kimberly Piermatteo:** OK. Thank you, Tim, and thank you, Andy. Does anyone else on the call today have any more questions that we would like to ask our panelists?

OK, we have another question coming in from ArionBio. Arion, I've unmuted your line. Please unmute yourself and ask your question.

**ArionBio:** Yes. You can hear me, right?

**CDR Kimberly Piermatteo:** Yes, we can.

**ArionBio:** Yes, thank you. So a question about the COVID and the flu combined test for rapid antigen test. So has federal FDA request all the tests on the same test cartridge, same strip, or can we split it into two different strips, so one for COVID, the other for flu, but we use the same sample collection?

**Timothy Stenzel:** So unlikely to be successful with two different tests, but the same collection because of the EUA authorities govern the pandemic virus, which is SARS-CoV-2. So if you can add additional analytes to SARS-CoV-2 tests, we have allowed that because it has SARS-CoV-2 on that test. But if you have ideas, you're always welcome to submit them as a pre-EUA to the FDA. And we will let you know whether your approach is acceptable.

**ArionBio:** I see. OK, thank you.

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

**Ezra:** Hi, guys. This is Ezra. Thank you for taking my call. A real quick question. Is there a template for the SARS-CoV-2, flu A, flu B combo OTC antigen test? Thank you.

**Timothy Stenzel:** If you look at the template for antigen tests, it will have recommendations for other viruses.

**Ezra:** Oh, you mean within the current antigen template.

**Timothy Stenzel:** Yes.

**Ezra:** OK, terrific. Thank you.

**CDR Kimberly Piermatteo:** Thank you, Ezra. Our next question is coming from Paul. Paul, I've unmuted your line. Please unmute yourself and ask your question.

**Paul Chapman:** Thanks very much. Paul Chapman from Domus Diagnostics. To the template for nucleic acid tests in a COVID multiplex, I can't find a number. I've got now number of positives required for COVID is 30. Flu A, 50. Flu B, 30. Do you have a number for RSV, or could you direct me to it? Thank you.

**Timothy Stenzel:** Yeah, I don't know that it's in there. Kris, can you provide any information on the call, or would you like an emailed question?

**Kristian Roth:** I think, from your perspective, you'd want to have an email because you'd want to have that in writing. But I believe we've been treating RSV similar to flu B. But again, I think you want to send that in and have that in writing from us before you go off and do a study.

**Paul Chapman:** Great. Alright, thanks very much.

**CDR Kimberly Piermatteo:** Thank you, Paul. Our next question is coming from Rakan. Rakan, I've unmuted your line. Please unmute yourself and ask your question.

**Rakan Qazziha:** Hello. Hi. This is Rakan Qazziha from Tracks Management Services. Thank you for taking my question. So my question is regarding that we applied for an EUA OTC antigen test this month, and we have a lead reviewer already assigned. So my question goes back to the timeline. So at the beginning of the call, I heard that the priority depends on the quality and content of the application. However, so this kit has been authorized in many international countries, all around the world, including Europe, Germany, Asia.

And we also have a CE IVD approval. We also conducted the clinical trials requested in different states in the U.S., in seven different locations. But due to the low positivity rate that we faced in the last three months, the trial took more than expected. However, we have completed everything, even much of the samples. We have gene sequence and we have omicron, detected omicron and delta variants.

So my question is, it's been, I think, around more than two weeks. So how does the timeline look like for a response, since the application is fully completed? And I heard in the previous Town Hall calls that, if a kit is already being approved in many countries, then it's given a prioritization.

**Timothy Stenzel:** Well, not necessarily. So the priority has to do with its impact on the pandemic response now and on volume and on the quality of the submission. So many of the other countries do not do a review of a submission. And so certainly if there is additional information that is available for the FDA to review from work outside the U.S., that is helpful.

So I think, as I've stated before, we have a 10-day review deadline. So typically, if you haven't heard from us in 10 days, we do a completeness check within 10 days. So if that's within, if now you have past 10 days and you have been assigned a reviewer, that's usually a sign that the file was judged to be complete, or at least all the elements that we expect to see are there. Whether they are properly done and executed or not is perhaps to be determined. If you've been assigned a reviewer, that's also a good step.

As I've noted recently, we are still seeing many, many, many EUAs, and a lot of them are antigen tests. And in fact, the bulk of the new submissions are in the antigen test area. So we have beefed up that team. We have shifted resources to make those reviews go faster. But we, unfortunately, cannot tell you how quick that is. And as we've said, if the submission is well-organized and the studies are well-written

and well-done, and there are no issues that are of significance, those applications do go through more quickly.

**Rakan Qazziha:** Great. Thank you very much.

**CDR Kimberly Piermatteo:** OK, we have time for one more question today. Dennis, I am unmuting your line. Please unmute yourself and ask your question.

**Dennis Repella:** Hi. It's Dennis Repella with Smith Associates, FDA Consultants. Earlier, there was a question about randomization in the clinical trial for the samples for the subject versus the comparator samples. And I believe in the response it was stated that the PCR sample should be taken secondly so that there's no training for the subject in the study.

Now, my question is, I can see where that would apply in the usability studies. For the clinical study, if the sample sites are different, usually the PCR samples are nasopharyngeal samples versus an anterior nasal sample that's in the antigen test. So I would think that the PCR sample could be taken first. And I believe it's also stated in one of the templates for study design for the antigen test. So if you could clarify that, that would be a big help. Thank you.

**Timothy Stenzel:** It does depend. If it can be done, we would prefer to see the molecular collection, the comparative collection done afterwards because there's both potential collection bias, in addition to other biases, such as interpretation bias. And we are looking for can somebody self-collect on their own, without any sort of instructions or training or coaching. And even if they take a mid- turbinate or a nasopharyngeal swab sample for comparator, they are seeing how the health care worker is handling a swab and doing the swabbing.

So that is what's preferred. There are situations like tests of record where some developers may be required to test the record first. And so if you don't do it the preferred way, I would just recommend that you touch base with the FDA, probably through a pre-EUA, to make sure that your plan is acceptable.

**Dennis Repella:** Well, one other point is that the comparator samples are usually put in a transport media and then taken away for testing, whereas the subject has to continue and actually self-test.

**Timothy Stenzel:** True.

**Dennis Repella:** OK. Thank you.

**Timothy Stenzel:** Mhm.

**CDR Kimberly Piermatteo:** OK. Thank you, Dennis. That was our last live question for today. I want to thank our panelists, Tim, Toby, and Kris. We appreciate everyone's participation today.

As I mentioned earlier, a recording of today's Town Hall and a transcript will be made available on CDRH Learn. Please visit CDRH Learn at the link provided on this slide. You will find the recording and transcript under the section titled Specialty Technical Topics, and then the subsection titled Coronavirus (COVID-19) Test Development and Validation Virtual Town Hall Series.

If you have additional questions about today's Town Hall and COVID-19 IVD topics in general, you may send an email to [CDRH-EUA-Templates@fda.hhs.gov](mailto:CDRH-EUA-Templates@fda.hhs.gov).

And lastly, please remember to join us for our next IVD Town Hall, scheduled for Wednesday, June 1st, 2022 from 12:05 to 1:00 PM Eastern Time. Again, thank you for joining us today. This concludes our Town Hall. And have a nice day.

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