Virtual Town Hall #75
December 15, 2021

Moderator: Joseph Tartal

Joseph Tartal: Hello, and thank you for joining us today. I'm Joseph Tartal, Deputy Director in the Division of Industry and Consumer Education in CDRH's Office of Communication and Education. And I'll be moderating today's program. Welcome to the Virtual IVD Town Hall Number 75 for SARS-CoV-2 test developers, in which we'll discuss and answer your questions about diagnostic tests in response to COVID-19. Today's presentation and transcript will be made available at CDRH Learn under the subsection title Coronavirus COVID-19 Test Development and Validation Virtual Town Hall Series.

Please note the November 17 program is posted and we're working to post the recording and transcript from the last Town Hall on December 1. We hope to post it this week. This is the last IVD town hall for 2021. The next scheduled IDV town hall will take place Wednesday, January 12, 2022.

Our panelists for today's program are Dr. Timothy Stenzel, Director of the Office of In Vitro Diagnostics and Radiological Health or OIR, in CDRH's Office of Product Evaluation and Quality; Toby Lowe, Associate Director for Regulatory Programs at OIR; and Dr. Kristian Roth, Deputy Director of the Division of Microbiological Devices, also in OIR. We'll begin with opening remarks from our panelists. And then we'll answer your previously emailed questions about COVID test development and validation.

Please note we receive some questions that are too detailed or test case specific that will not be addressed on the call. For those questions, we will try to send a response in writing within a few days. If you submitted a question and do not hear it address, please look for the written response. If you do not receive the written response in a few days, please feel free to reach back out to cdrh-eua-templates@fda.hhs.gov for an update. Then last, we'll open up the line for your live questions.
Now I'm going to hand over the program to Tim. Welcome, Tim.

Timothy Stenzel: Thank you. And welcome, everyone, to this edition of the town hall. We welcome your questions ahead of time, which we've prepared answers to for many of them. We've prepared answers to others, but they're so specific, we will email those to the submitters. And then we'll open it up for a live Q&A.

I think, again, the topic of the day is omicron. And I want to start out with an omicron update. We are receiving a lot of inquiries about this variant. We continue to monitor viral mutations and variants and the potential impact on SARS-COV-2 diagnostic tests, as well as serology tests.

However, we're primarily continuing to focus most intently on molecular and antigen tests. And we work closely with test developers, as well as NIH RADx, their variant task force, and the CDC on these to assess impacts. We have today updated our website, our SARS-CoV-2 viral mutation website, with a couple of modifications.

We will continue to update the website as a new and important information is gleaned. Sometimes we'll do something out of an abundance of caution. Others we will update for information that we think is critical for you all to know.

We have updated the list of tests that we believe will fail to detect omicron. And so there are now three molecular tests. You can go to the website and see all three. Fortunately, we think that these are still relatively low abundance, relatively low volume, not extremely low, but not high-volume tests and services. So the impact on the overall national response we hope is muted.

The new addition is the test that actually has two targets. And it is then our first two-target assay that fails to detect what we believe is going to be a significant variant in the US in very short order. We are recommending these tests should not be used until the issue about omicron is solved.

Our work with antigen tests continues. It is dependent on actually acquiring both developers and/or the US government acquiring omicron samples and being able to test them in the lab and determine their reactivity for that test. So stay tuned on antigen tests.

We also have updated the list of for gene dropout. We've added to the S-gene dropout list. In addition to the S-gene dropout list, we've now added an N-gene dropout list. And there are two tests that are EUA-authorized that we believe will have a dropout of the N-gene, which is a unique marker. At least in deletion 31 to 33 in the N-gene is a unique marker for omicron.

And these two tests drop their N signal and retain their other signaler signals in the face of a SARS-CoV-2 omicron infection. So just like the S-gene dropout, the N-gene dropout may be helpful in identifying samples where omicron may be present so that sequencing can be considered to characterize the variant. One thing with the S-gene dropout is that there are two main sublineages of omicron, VA1 and VA2.

We're primarily, at this point, we think, seeing only VA1 in the US. But VA2 may enter the US or may already be here. And only the VA1 has the S-gene dropout. The VA2 does not. However, both sublineages do have the N-gene dropout.

The challenge here is not-- S-gene dropout is not present, perhaps, we don't think, in all the VA1s. And nor is N-gene dropout present in all the VA1s and in all VA2s. So these are not ideal markers. And obviously, because S-gene dropout can happen with something that's not omicron, just having an S-gene dropout doesn't automatically make it omicron.

It would be uncommon, but there is enough cases of delta circulating with S-gene dropout, that it could confuse the situation. N-gene dropout, however, at the moment, at least, we think if you see N-gene dropout, that would be a positive ID for omicron, to our understanding at the moment. But again, the problem is it's not present in all omicron samples. And therefore if you're missing S-gene drop-out or if you're missing N-gene dropout, it doesn't rule out omicron.

Sequencing remains the gold standard. I'll go into that a little more. But do see the updated website with regard to the both now N-gene dropout tests and S-gene dropout tests. Talking about genotyping or sequencing, for a long time now, we have had conversations with some developers of high-volume genotyping assays and given them our thinking on recommended validations.

As I said, whole genome sequencing remains the gold standard. I'll kind of go into that in a little bit. But with sequencing, everybody knows the turnaround times and the throughput that sequencing assays have remains challenging when you want to determine genotypes for a large number of samples. So test developers that are interested in developing new assays or have assays already developed that do

genotype, you can approach the FDA and receive validation recommendations that have given to others previously who had submitted their interest to the FDA by sending an email to covid19dx-- all one word, no hyphen, So covid19dx@fda.hhs.gov.

So one clear challenge for any developer of the genotype assay is deciding which markers they want to use today. Do you just use, say, delta and omicron markers? Or do you also include the previous variants? Well, the previous variants may not return.

So taking up real estate on an assay for previous variants may not be a good decision. And we're not talking about what the FDA advises or doesn't advise here. What we are saying is that this is, just by nature of the science and this virus, a challenge for any test developer to understand. And then if you have a set of genotypes for everything that's currently known, what happens when you get a new variant that has a new marker that's important to measure?

How do you update your assay and how quickly? And because these variants and mutations, in many cases, seem to come and go, the panel of genetic markers could be shifting a lot more quickly that we've seen, than we would like, making a challenge to keep these assays up to date. And so those technologies that can be updated quickly may be more ideal than other technologies. So those technologies that you can swap in and out assay targets, primer and probe—

Toby Lowe: Tim, did you accidentally go on mute? Or did you somehow drop off?

Timothy Stenzel: Sorry. I'm still on. My internet is going in and out for Zoom. Where did I leave off?

Toby Lowe: You're talking about the ability to swap primers and probes, I believe.

Timothy Stenzel: OK. So those technologies that are able to swap out primers and probes and do not affect the other primers and probes, everything that's in bulk in a master mix is going to be a little bit more challenging to revalidate. So those technologies may have-- are more ideal for this type of situation than those that may require more challenging validation. The FDA will welcome submissions that include a request for preauthorized change modification procedures.

And simply put, if you have a technology that you may want to update when the next variant comes along, should it come along, which presumably it will, but when the next mutation comes along, which is likely to happen, how do you alter your assay for that? What are the validation recommendations? What are the results of those validations that would allow the FDA to quickly or without a formal review because it meets the pre-change-- pre-specified change outcomes to go ahead and launch that?

Anyways, we'll entertain those requests because of the necessity. When you're developing genotype assays for this virus, as has been proven time and time again, that the genotyping assays will need to shift, depending on what we're currently seeing in the US. Nonetheless, if and when genotyping becomes clinically important, the need will be for a high volume, fast turnaround time, and accurate tests.

So if there is a true need clinically, then we'll want essentially all positive patients in the US to be able to be tested for that. So that is the challenge, to generate those high-volume, fast-turnaround time, and accurate tests. That's about what I wanted to say about omicron. It's a lot. It remains a very high focus

throughout each day basically since Thanksgiving Day for us. So I'll turn it over to Toby. She has additional prepared remarks. And then she'll go into the prepared Q&A.

Toby Lowe: Thanks, Tim. So I just have one topic to talk about briefly before we get into the prepared Q&A. This topic has come up a lot with our review of clinical validation and it's regarding the different indications for screening indications of asymptomatic individuals versus symptomatic or those suspected of COVID-19. So what we recommend is that when you submit-- or when you're doing your studies and then when you submit your data, that you record whether each subject is symptomatic or asymptomatic, as well as whether they have a known exposure or not. And then include your data stratifying by these designations.

So generally, if you are seeking a screening indication, so an indication for testing individuals who do not have symptoms or other epidemiological reasons to suspect COVID-19, we would consider your data on subjects who are asymptomatic with no known exposure. On the other hand, for an indication of individuals or for individuals suspected of COVID-19, we would consider data from symptomatic individuals, as well as asymptomatic individuals with a known or suspected exposure. So with that, Joe, I can turn it back to you. And thanks for helping us with the prepared questions.

Joseph Tartal: Sure. And thank you, Tim and Toby, for those updates, some very important updates there. So with that, we're going to get into the first emailed question. And that is, can test developers offer their tests if an emergency use authorization EUA request is submitted within 60 days of the policy for coronavirus disease 2019?

Toby Lowe: Thanks, Joe. And I just want to note that this specific question was actually referring to a multi-analyte COVID and flu molecular test. And so I know that question has come up previously. So I want to make sure that we include that note in our response as well.

And so generally as described in the updated policy for coronavirus tests, the guidance that was updated on November 15, for tests that were developed by a high-complexity CLIA-certified lab and used only in the lab in which it was developed, so generally an LDT, that were offered for clinical use prior to November 15, the date of the guidance update, FDA does not intend to object to developers offering the tests while FDA reviews the EUA requests, provided the EUA request is submitted to FDA within 60 days of that guidance posting on November 15, and as outlined in the guidance. So there are a lot of details in the guidance about that process. For newly developed and not-yet-offered tests, so those that a lab or other developer might develop after November 15, we do expect those tests to receive an EUA prior to being offered for clinical use.

Joseph Tartal: OK. Thank you. That's a very comprehensive answer. So we'll move to question number two. Can manufacturers implement device modifications while the emergency use authorization supplement is under FDA review?

Toby Lowe: Thanks, Joe. So the Section 4D of the policy for COVID tests that was updated on November 15 does also address modifications that were made before and after November 15. There are some slight differences to those policies and the types of modifications for which the FDA does not intend to object to implementation of the modification to the diagnostic test while FDA conducts its review. It's important to note-- and this is discussed in the guidance-- that such tests, the use of those modified tests is limited to use in a high-complexity CLIA lab, since the modified version of the test is not yet

authorized. And the guidance also discusses certain measures that a developer should take to provide transparency.

And the original question for this one also asked about whether labs that use this modified test need to submit their own EUA request as an LDT? And that is generally not expected. While the modified test is not considered to be authorized, if it's being offered under the modification policy in the guidance, the FDA does not expect laboratories that are using the test to submit their own EUA request, as long as they are using the test as provided by the manufacturer with the modified instructions that include the discussion of the modification and the modified performance and that it is still under FDA review.

Joseph Tartal: OK. So we'll move on to our next question. Will FDA consider over-the-counter, OTC, multi-analyte tests for asymptomatic individuals?

Toby Lowe: Yeah. So we have previously discussed this on the Town Hall and in other venues. And we've previously indicated that we were not at that time interested in over-the-counter multi-analyte tests. We are now considering whether there is an appropriate pathway for such tests. And we recommend that test developers interested in an over-the-counter multi-analyte test submit a pre EUA to further discuss your proposal.

Timothy Stenzel: And Toby, I'll just add to that. We still have no idea what an asymptomatic flu test result would mean clinically, if it were even to occur. So perhaps there are folks with data out there. But there are different ways to handle this. But what we're signaling very clearly is that an OTC model for a multi-analyte test that would be covered under the EUA provisions, we look forward to seeing a pre EUA to describe your plan.

Toby Lowe: Thanks, Tim.

Joseph Tartal: Good to hear. Next question, what documents are required to support a Laboratory Developed Test, LDT, EUA authorization? And this question actually has several parts. So I'll ask these all together. Do we need an instruction for use, IFU document, or an EUA summary? What if the test is performed in multiple different CLIA-certified laboratories in different locations? So there's a lot here.

Toby Lowe: Yes, this is a complex question. So generally, all test developers, including laboratories that are submitting an EUA request, may use the optional EUA templates. Those are provided on our website. And they generally recommend providing information on the indication of the test, a description of the test, the validated performance of the test, a description of how the test was validated, and the validation data.

Alternatively, the COVID test guidance discusses for laboratories that they may submit an email, and even the template, the submission does go through an email to the FDA. But the other option is to submit an email to the CDRH EUA template mailbox, with supporting information such as a description of the test and the intended use, and attach existing validation test reports and Excel data files that the lab may already have on file in accordance with their internal procedures. A lab that has developed their own test may also consider whether their test meets the criteria for inclusion in the umbrella EUA for SARS-CoV-2 molecular diagnostic tests for serial testing. That was issued also on November 15 when we updated the guidance.

And we would recommend that laboratories review the criteria included in the EUA letter of authorization for that umbrella EUA. If a laboratory test meets the inclusion criteria and they would like authorization under the umbrella EUA, they just need to follow the instructions in the letter of authorization for submitting information to FDA. And then regarding documentation, for LDTs, which are tests that are designed, developed, and used within a single high-complexity CLIA-certified lab, typically the laboratory developer provides their laboratory procedures to accompany the EUA request in lieu of an IFU, or the instructions for use, that we would typically see with a commercial distributed test kit. Upon authorization, FDA would then post an EUA summary, including information about the tests performance. And this labeling approach may also be used for certain tests developed by laboratories that are distributed and performed in multiple laboratories.

Joseph Tartal: OK. Great answer. And we'll move on to our last emailed-in question. Does FDA's current priorities extend to amendments and revisions for already existing EUAs?

Toby Lowe: So we do consider each submission, including amendments or supplemental EUA requests independently when determining the priority for review. So we consider whether the submission at that time is within FDA's priorities that are described in the test guidance, the test policy guidance.

Joseph Tartal: OK. So that is the end of our emailed questions. And please remember, as we noted earlier, if we did not answer your question on the call, it's likely because there was a lot of detail, or it was test or case specific. And we will be sending out an email response to you. So please keep a lookout for that email response.

And now we'll move on and take your live questions. So to ask a live question, please select the "Raise Hand" icon at the bottom of the screen. When you are called on, please identify yourself and ask your question promptly. Also, please note we're not able to discuss specific submissions that are currently under review. So we have a few people already with their hands raised. So I'm going to start with the top. So Brigid, I'm going to unmute you. Please unmute yourself and ask your question.

Brigid Bondoc: Hi. This is Brigid Bondoc from Morsen and Forrester. Thank you, Tim and Toby, for your continued support of test developers and for your time during this afternoon's town hall. Updated guidance from the Agency that was published on November 15 outlines a series of COVID-19 diagnostics that are eligible for priority review.

Outside of those listed, I wanted to inquire regarding the Agency's willingness to review other types of tests that would support its patient safety and public health mission by driving access to high-quality, accessible testing in non-clinical, non-at-home settings. In particular, would the Agency be willing to review a fully automated high-throughput COVID-19 test device that could be used in settings such as schools or corporate lobbies, analyzing self-collected specimens? And if yes, would this be something that the agency would consider for priority review? And are there certain components to the product development or user comprehension studies that the agency would like for developers to consider?

Thanks so much.

Timothy Stenzel: Yeah. You'll probably want to send in a pre EUA with details. But to me, it sounded like there was an instrument. And it would operate at a school, and it would return results to individuals. That would more than likely fall under the point-of-care test category to be used in locations that have a

CLIA certificate of waiver, or they could be moderate or high complexity. Once we authorize for a point-of-care setting, then they can be used in those settings.

Tasks that can be performed entirely by individuals themselves and interpreted by themselves at such locations, such as schools and workplaces, would fall into the over-the-counter category. However, it does need to be a device that can be wholly operated by the subjects themselves and not require more of a laboratory setting, even if it's a CLIA way laboratory. Hopefully that addresses your question enough on this call.

Brigid Bondoc: Thank you so much.

Joseph Tartal: Thank you. We'll go on to our next question. Eveline Arnold, I'm unmuting your line. Please unmute yourself and ask your question.

Eveline Arnold: Yes. Hi. This is Evelyn Arnold. Can you hear me?

Joseph Tartal: Yes, we can hear you.

Eveline Arnold: OK. Great. Yes, sorry. I had some audio connection problems earlier. So, yes, hi, my name is Eveline Arnold. I'm here on behalf of Tempest Laboratories. Thank you to Toby and Tim again, especially for your clarification surrounding the section of the guidance pertaining to modifications. We do actually have a few questions that are all related to modifications. So I will try to get through them, since they're relatively short.

So number one, we do have a question regarding the addition of additional laboratory facilities to a previously authorized EUA. These are facilities that are owned by Tempest, and they would adhere to our EUA requirements in our previously authorized EUA. And so we do have a question on what we would need to do in order to make this change to add these facilities? And secondly, if we need to wait for authorization prior to implementing this change to add facilities?

Timothy Stenzel: So Toby, you want to handle that one?

Toby Lowe: Sure. So for an addition of additional labs, we would expect you to send in a supplement. And Kris, I'm going to ping to you as well because I'm not sure if we ask for additional reproducibility data when we're adding additional labs.

Kristian Roth: Not that I'm aware of, no.

Toby Lowe: OK. So we would probably want to see in your submission some information about how you're going to ensure that the other labs are performing the test according to the authorization.

Timothy Stenzel: And adding—

Toby Lowe: Oh, go ahead. Go ahead.

Timothy Stenzel: I was going to say and adding an additional lab isn't covered in the updated LDT policy of November 15. So adding that additional lab will probably-- because it falls outside this category that we think of as an LDT, as developed in a single lab, and often a single lab. In all likelihood, you're going

to want to have authorization before you add that additional lab. But come in with a pre EUA, and we'll confirm that.

Eveline Arnold: Thank you. And if you don't mind, I do have two additional clarifications surrounding modifications. I can do the second one. So we would also like to clarify if EUAs with changes made after November that include new instruments and reagents can be continued to be offered with the modification while under review just like new EUAs can be offered while the submission is under review? And this is based off of our understanding of Appendix B of the revised guidance document. If you could speak to that, that would be helpful.

Timothy Stenzel: Yeah, Toby, you might be the best to answer that clearly.

Toby Lowe: Yeah. I'm not sure I fully that the situation you're talking about. Modifications that are made after November 15?

Eveline Arnold: Yes, these are changes that we made or are planning to be made after release of this new guidance, or of the updated guidance. I'm not sure if I can provide more description than that.

Timothy Stenzel: Yeah. I think that may require a pre--

Toby Lowe: That would fall under--

Timothy Stenzel: Yeah. If you've got a submission before the FDA, then you can talk to your reviewer about these modifications. I think the modifications part of the LDT updated policy had to do with whether the performance of the test indications for use would change. Or minor modifications may be just fine for what you're talking about. It all depends on the details.

Eveline Arnold: Yes. I do think it's-- Sorry.

Toby Lowe: Follow Section One. As long as it's not changing the indications for use or the analyte-specific reagents, and that you've submitted the modification in a supplemental EUA request.

Eveline Arnold: I see. I am thinking-- our question arose from the portion that was not specifically called out in the guidance. It seems our interpret-- our understanding, then, based off this response is that, I guess, will we be able to continue offering this? Or do we have to basically see a--

Timothy Stenzel: It depends on the details. If you've submitted, already talked to your reviewer, they'll raise it up for discussion. OK?

Eveline Arnold: OK.

Timothy Stenzel: Is the next one quick? Because we do have a long line of callers--

Eveline Arnold: Yeah.

Timothy Stenzel: --with questions.

Eveline Arnold: I do appreciate it. A clarification regarding the minor modifications, as spelled out in that section of the guidance. If they do not impact the indications for use or the performance of the assay, are we correct in understanding that we can make this without a change-- without a notification to FDA, or a new EUA?

Toby Lowe: I think these are probably so detailed that we would suggest that you send it in, either to the mailbox or your lead reviewer and take a look.

Eveline Arnold: OK. Appreciate it. Thanks.

Joseph Tartal: Thank you. Evelyn. Our next question is from Thomas. Thomas, I'm unmuting you. Please unmute yourself and ask your question.

Thomas Roades: Hello. This is Thomas Roades from the Duke-Margolis Center for Health Policy. Thanks to the whole FDA team for facilitating these town halls. I wanted to inquire as to the possibility of rapid test manufacturers extending expiration dates. Is that something that FDA is considering offering flexibility on at this time?

Timothy Stenzel: Oh, we're very supportive of them extending their dates. And there's a process to do that. We expect them to collect data. And as soon as they have the data, it'll be a quick review by the FDA to see if the test is still stable to their most recent testing time point. And then the FDA gives authorization for them to update their expiration dates. We have been very flexible in the past, and will continue to be very flexible with kits that are approaching the original expiration dates in the field, with having the test developer notify their customers of the updated expiration dates for those kits, and any unused kits in the field, by lot number.

Thomas Roades: Great. Thank you very much.

Joseph Tartal: Thank you. Our next question is going to be from Diana. Diana, I'm unmuting your mic. Please unmute yourself and ask your question.

Diana: Hi. Good morning. Thank you so much for allowing me to ask. I'm with PerkinElmer, and we do contracting with Hub Labs for COVID testing, molecular diagnostic testing, using our EUA-approved molecular diagnostic assay. We are working with one lab that is deviating from our IFU, just with respect to the PCR instrument they're using, as well as the volume of one of the controls, and the transport media that they're using. We want to know, would this be considered, automatically, an LDT, and this lab would need to submit as an LDT, because they are deviating from the IFU, with respect to one piece of equipment and two of the reagents?

Timothy Stenzel: If it's not authorized, and you haven't validated it, then that's definitely, definitely in the gray zone, if not further. It's probably best to check with our team. Typically, if a lab modifies, significantly, an EUA authorized device, then there are some modifications that the FDA would like to see. Toby, do you have any more definitive answer at this time? I think some of the details might be needed.

Toby Lowe: If you take a look at the guidance, it does spell out that there are differences between the policies for commercial manufacturers modifying their test, and a high-complexity CLIA-certified lab modifying an authorized molecular diagnostic. If the lab is modifying the test, and it meets the

description in the guidance, so it's not changing the indications for use or the analyte-specific reagents, we would not expect a notification to FDA or a new EUA from the lab, as long as the lab has validated the modification, and confirmed that the performance of the modified test is equivalent to the performance of the authorized test, and the use of that modified test is limited to the high-complexity CLIA lab in which the modification was made. We would also expect that lab to provide transparency about the fact that it is not an authorized test at that point, and that it has not been reviewed by FDA.

Diana: Thank you very much.

Joseph Tartal: And with that, we'll take our next question. Lisa, I'm going to unmute your mic. Please unmute yourself and ask your question.

Lisa Baumhardt: Hi. Thank you, Tim and Toby, for taking time to answer my question. My name is Lisa Baumhardt, and I'm with Hyman, Phelps, & McNamara. My question has two parts, and it's related to the November 15 revisions to FDA'S EUA guidance.

The first part is, can you comment on the changes that an EUA holder for a molecular assay, that is not a CLIA lab, a commercial manufacturer, can make without needing to submit a supplement to the FDA?

And then my second part is, is it possible for an EUA holder to implement newer versions of instruments while the FDA's review of an EUA amendment is pending? Thank you.

Timothy Stenzel: Toby, can you take a first stab at this?

Toby Lowe: Lots of modification questions today.

Timothy Stenzel: Yeah.

Toby Lowe: You're talking about a commercial manufacturer making modifications to their authorized test.

Lisa Baumhardt: Correct. Go ahead.

Toby Lowe: We would expect-- this would fall under the modification section in the guidance, again. You asked-- I think you said, specifically, implementing newer versions of instruments. That would fall under the policy where we've noted that if it does not change the indications for use or the analyte-specific reagents, so as long as the manufacturer submits their validation data to FDA in a supplemental EUA request, then we would not object to that modification being implemented while FDA reviews.

But again, noting what I had said previously about the transparency. And that's all discussed in Section IV (D) of the guidance. And I think you also asked about what changes could be made without any submission to FDA.

Lisa Baumhardt: Correct.

Toby Lowe: Is that the other part?

Lisa Baumhardt: Yes.

Toby Lowe: The letters of authorization do spell out fairly clearly what can and can't be done. The guidance is just providing a little bit of flexibility on that. So I would take a look at your specific letter of authorization, and if there is a specific modification that you're not sure about, I would send in the details about that. But generally, we do expect a supplemental EUA request for modifications.

Timothy Stenzel: If they're swapping a vendor, but it's the very, very same component, it's the same type of swab, just a new vendor, there are some things that the FDA doesn't need to see, unless it changes the performance. Do look at the policy, and you can follow up with more specific questions to our template's email inbox.

Lisa Baumhardt: Thank you very much.

Joseph Tartal: Thank you, Lisa. Our next question, Gitte. I'm going to unmute your mic. Please unmute yourself and ask your question.

Gitte Pedersen: Thank you, everybody. My name is Gitte Pedersen from Genomic Expression, and we started-- very early, couldn't get any reagents, so we had to develop our own LDT, I'm the CEO of a CLIA Lab in Boston. And we were in review late-- or actually mid-2019. And in late 2020, FDA decided not to pursue review of LDTs. And I think I'm hearing, now, that that has been reversed.

And I sent in some questions. What I was able to read was that it's the States that have the responsibility to oversee our testing at this point. But from some of the answers, it also sounds like we need to engage with the FDA again. Just for clarification, we are operating under the SalivaDirect umbrella EUA. We are operating in saliva, as well as NP swab. Thank you.

Timothy Stenzel: Anything that's authorized under the SalivaDirect, and SalivaDirect has authorization, and you follow their protocols, and they have designated you as a SalivaDirect lab, the FDA has authorized SalivaDirect to make those designations, and those labs, performing the procedure as indicated, are covered by the EUA. Any significant modifications would not be covered, as we've previously covered on this call.

In addition-- and Toby, you'll remember the States-- there were States prior to the point after the HHS statement in August of 2020 where the FDA, at that point, after that statement by HHS, decided not to review LDTs. When that HHS statement was-- when the current HHS restored LDT oversight to the-- clearly restored the longstanding policy of HHS and FDA on LDTs, when that was restored, clearly, on November 15, then the FDA picked up review or authorities for COVID tests.

Again, if you're doing SalivaDirect, you're following their procedure, you're a designated lab, no EUA is needed. There are States that, early on in the pandemic, we allowed to review tests within their States without requiring FDA review. And those are not EUA-authorized tests. But those States that had been previously designated when the policy was updated on November 15, those states could continue to do that. Toby, anything different, or updates that you want to make?

Toby Lowe: Yeah. I can just add a little bit more there. First, on the States issue. I think you said you were in Boston. Massachusetts is not one of the States listed on our FAQ page as a state that had notified us that they were choosing to authorize labs within their state to develop and perform tests.

But we do have information on that policy, both in the FAQs on our webpage, and in the November 15 guidance.

From a more general perspective, it sounded like you were saying that you have your own LDT that you're performing with NP swabs, and then you're also performing the SalivaDirect test with saliva samples. As Tim said, the SalivaDirect test is an EUA-authorized test. It is not an umbrella EUA. That has been a point of confusion, so I just want to throw in that clarification. It is an authorized test that is authorized for the protocol to be distributed to labs that SalivaDirect designates to receive their protocol and perform their test. If you are designated by SalivaDirect, and you're performing their test as authorized, as Tim said, that is an authorized test, and there's nothing that you need to do, additionally, for that.

For your LDT, if you're performing your own LDT, I would suggest that you take a look at the November 15 guidance document, and, specifically, take a look at Section IV.C. And most likely it's going to be IV.C (2) for you, since you would be considered a test, an LDT, that's being offered without FDA authorization, following the HHS August 2020 announcement.

As described in that policy, we would expect you to submit an EUA request to FDA for your LDT within 60 days from the date of issuance of that guidance. I believe 60 days from that is January 14.

Gitte Pedersen: All right. Thank you so much. That was very clear.

Joseph Tartal: Thank you, Gitte. Next up is Ron. Ron, I'm unmuting you, so please unmute yourself and ask your question.

Ron Domingo: Hi. This is Ron Domingo from Precision For Medicine. We would like to submit a premarket submission for our OTC COVID-19 test, and would like to know if this could be submitted as a 510(k), or would this be a De Novo? Thank you.

Timothy Stenzel: Is it a molecular test or an antigen test?

Ron Domingo: It's an antigen test.

Timothy Stenzel: Yeah. We haven't fully authorized-- granted a De Novo for an antigen test. Such a submission, in all likelihood, should be a De Novo. Once we authorize the first De Novo, every subsequent test would be a 510(k).

In the process of reviewing the first De Novo in a category-- we haven't done antigen yet. Serology would be the same boat-- we look at what mitigations are needed to ensure safety to down-classify, to class two, for the device. We put those mitigations in a document called special controls, that all subsequent developers know how to validate, and what factors are important for risk mitigation for that test. It would be a De Novo application for you.

Ron Domingo: All right. Thank you.

Joseph Tartal: Our next question is from Rachel. Rachel, I'm unmuting you. Please unmute yourself and ask your question.

Rachel Liang: Hi. Thank you for taking my question. The guidelines for the molecular template ask test developers to recruit four to six test operators for the clinical evaluation study. And these individuals should be, I believe, trained in patient care, but not laboratory-trained. Our question is, would it be acceptable to onboard medical assistants, specifically, as test operators for a point-of-care clinical trial study with a molecular test?

Timothy Stenzel: Yeah. I think what you're talking about, can you create a pseudo point-of-care setting within your company by recruiting talent to do that testing in your setting. What we're really looking at is, in a real-world setting, a busy clinic, that's seeing multiple patients each day, and also doing testing, if they choose to do that at their site, in a CLIA-waived lab, can they accurately do the testing while they're juggling all the other clinical balls that they have to? It makes it imperative that the point of care test is super easy to perform and hard to mess up on the performance of the test and in the interpretation of the test.

The templates are quite clear on the point of care settings and the number of individuals. I think we have allowed as few as one site, although we want to see multiple operators at that site so that they just don't use an expert person who knows how to do point-of-care tests because of their experience. But we see a wide variety of folks in that particular office and site.

But we do encourage more sites. But do look at the templates, at those requirements. And if you have any questions about our templates, recommendations, you can send that question into the EUA template email address.

Rachel Liang: Sure. And just to clarify, we were looking at two different clinical sites. But right now, we're having some difficulty onboarding these nurses and doctors and PAs. So we were wondering if it's possible to-- if it would be acceptable to onboard medical assistants, specifically, as test operators.

Timothy Stenzel: I think what you're—I probably misunderstood your question. At these point of care sites, is it OK for medical assistants, who are already employees of those sites, to do the testing, instead of others.

Rachel Liang: Right. Right.

Timothy Stenzel: Yeah. Yeah. The FDA doesn't specify training or education levels for that. We don't want to see trained laboratorians. At those sites, they can choose whoever they want to at that site. If their background is such that they wouldn't normally be doing these things, that does put you at a slight disadvantage if the test isn't super easy to perform.

Rachel Liang: OK. OK. OK. Thank you.

Joseph Tartal: Let's get to our next question. Annie, I'm unmuting you. Please unmute yourself and ask your question.

Annie, are you there?

Annie Wright: Hi. Can you hear me?

Joseph Tartal: Yes.

Annie Wright: Can you hear me?

Timothy Stenzel: Yes, we can.

Annie Wright: Yes. Hi. Hi. My name is Annie Wright, and I'm from Wondfo USA. Thank you for taking my call. We're in the process of doing a clinical study for our rapid antigen for OTC-use product. And I was wanting to know about the serial testing portion of it for asymptomatic patients.

In the EUA template, it basically instructs us to talk to the FDA reviewer and make sure that we present our study design and get that approved by the reviewer prior to implementing the tests. Our interpretation of that is that we will conduct all our testing for asymptomatic just as normal, without the serial testing portion. And then, when we submit our EUA, we can then discuss that with our reviewer, our assigned reviewer. Is that a correct interpretation?

Timothy Stenzel: I think so. We recommend that anything that doesn't follow the recommendations of the templates, that you check with the FDA before doing so. The serial testing is really to allow developers that have validated their test only on symptomatic individuals, with acceptable performance with the lower bound of the PPA, at least 70%, to be able to offer an asymptomatic screening claim, only with symptomatic data, as long as they instruct users to do serial testing with that test. If the developer wants to avoid the requirement for serial testing, they want a single test for an asymptomatic screen, then we want to see data in the truly asymptomatic population. And please note Toby's comments at the top of the hour, at the top of the meeting, about how we define asymptomatic.

Annie Wright: Yes. Correct. Yes. Our plan is to basically submit with the asymptomatic, the 30 negative, 30 positive for symptomatic, and then 10 asymptomatic. Is that acceptable? Would that be acceptable?

Timothy Stenzel: I believe that still holds.

Annie Wright: And then we would continue our study.

Timothy Stenzel: There's a commitment to do additional-- Yeah. Yeah. Exactly.

Annie Wright: Do additional. Yes.

Timothy Stenzel: Exactly.

Annie Wright: OK. And then, if needed, we would discuss the serial testing. Because we don't necessarily have to do it, right? Before we submit? I just want to confirm that.

Timothy Stenzel: Yeah. If you don't have enough asymptomatic data, you can start out with that. But then, when you get enough, it can be converted, if performance is adequate. OK?

Annie Wright: OK. But we have to get 10 asymptomatic before we submit. Or can we discuss that?

Toby Lowe: No. You can-- if you take a look at the serial testing template, I think it will clarify your questions. You can submit with just symptomatic data, and that's when we would add the serial testing to your indication.

Timothy Stenzel: Do 30 symptomatic and 30 negatives, minimum. If performance is good enough, we can give you the serial testing claim without any asymptomatic data. And then, when you accumulate 10 patients and perform on asymptomatic patients with adequate performance, we can review that and update your authorization later.

We are going to need to move to the next two callers, Joe. I hope we can go just a little bit long. I know that Pauline and Geetha had waited until 15 after the hour. I think Joanne got in after. So I would love to be able to try to address Pauline and Geetha's questions, and we won't probably be able to get to Joanne. But anybody who doesn't get their question asked and answered can submit an email to the template's email inbox, or submit a question prior to the next meeting by the due date, and we'll address it at the top of the meeting.

Joseph Tartal: OK. We'll try to get to Pauline and Geetha. Pauline, your mic is unmuted. Please unmute yourself and ask your question.

Pauline Gee: Yes. This is a very simple question. This is Pauline Gee from Ovation. And one of our labs is wanting to know whether we can actually do a bridging study to use an EUA test that has some expired reagents in it. Because, as you know, the testing actually dipped in terms of volume, and now it's back up again. And so if we can actually do a bridging study to show that the performance criteria is still met according to the EUA, are we able to use those reagents?

Timothy Stenzel: Are you a lab wondering if you can use expired reagents?

Pauline Gee: Yes.

Timothy Stenzel: Yeah. I would contact the developer, and also contact the FDA. We do not recommend using expired reagents. You'd basically have to do a full QC test, as the manufacturer would, on a daily basis, to know if you can trust the results each day. It's just not worth it. It's just not practical. And the manufacturer isn't guaranteeing that those products will be functional and sensitive enough beyond the expiration date. So the FDA does not recommend that.

Pauline Gee: Thank you.

Joseph Tartal: Our last question of today is Geetha. I am unmuting your mic. Please unmute yourself and ask your question.

Geetha Rao: Thank you. Thank you, Toby and Tim, and everyone for your continued Town Halls. These are incredibly valuable. I have a relatively, hopefully, simple question. I'm working with an LDT company that had previously submitted a request on an LDT template last year, and was then declined-- the FDA declined to review it, and the company has now been marketing the LDT.

Unfortunately, it's not in one of the States that is doing its own authorization. So we will be required-- we will be submitting an EUA request, hopefully just the additional documentation that's mentioned in the guidance. Toby, you had explained exactly where to go for that. My question is the following.

Two really quick questions. The first is, when we file this information, should this be a supplement to the original EUA number that we had received, or the original EUA that we filed? Or should this be a brand new EUA?

Timothy Stenzel: If the data is all the same, I think you can just notify us to look to that file. If you made any changes, we will want to see the modifications. The validation and the modifications. But again, refer to that first submission, the first EUA number, so that we can be as efficient for you as possible.

Geetha Rao: OK. Thank you so much. Yeah. That was the first--

Toby Lowe: Yeah. And, really quick--

Geetha Rao: Go ahead.

Toby Lowe: And you don't need to worry about the administrative side of things. Just send in your EUAs, your EUA requests, your data, and make sure to reference that you had the previous EUA, and whether any of the information in the previous EUA request is still current, still accurate. And we'll take care of whether it's reopening as a supplement, or whether we're creating a new EUA number for you. We'll take care of all that.

Geetha Rao: Terrific. Thank you so much. And then the follow-on question you've essentially answered is, there might be a couple of small modifications, and then there's also a plan to submit-- to offer the test for home collection. I assume that would be a separate EUA?

Timothy Stenzel: No. It would be--

Toby Lowe: You can submit all of that all together.

Geetha Rao: All together. OK.

Toby Lowe: Yeah. We would just ask that you not do the home collection until you get authorized because that's not considered an LDT.

Geetha Rao: Oh. OK that's really helpful. Thank you. We're going to try and get everything before the January 14 deadline to you, and then we'll take the home collection from there. OK. Terrific. Thank you.

Joseph Tartal: Thank you. That's our last question of the day. And thank you, everyone, especially our panelists, for answering all of those questions. We greatly appreciate everyone's participation. Today's program and transcript will be made available at CDRH Learn. Please visit CDRH Learn at www.fda.gov/training/cdrhlearn. You will find the recording and transcript in the subsection titled Coronavirus COVID-19 Test Development and Validation Virtual Town Hall Series. We are working as quickly as possible to post all of the programs.

For additional questions about today's town hall and COVID-19 IVD topics in general, please email cdrh-eua-templates@fda.hhs.gov. As we continue to hold these virtual town halls, we appreciate your feedback about the program. Please complete a brief survey, which you can find at www.fda.gov/cdrhwebinar. As a reminder, please join us for the next IVD town hall, scheduled for Wednesday, January 12, 2022. This concludes today's program. Thank you.

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