Virtual Townhall

Moderator: Irene Aihie
July 14, 2021
12:15 pm ET

Irene: Hello. Welcome to the FDA 63rd in a series of virtual town hall meetings to help answer technical questions about the development and validation of a test for SARS-CoV-2 during the public health emergency. Today, Dr. Timothy Stenzel in the Office of Product Evaluation and Quality and Toby Lowe, associate director of radiological health will provide a brief update. Following opening remarks, we will open the line for your questions developing the test for SARS-CoV-2. To ensure that we answer questions from as many people as possible, we ask that you use the raise your hand feature. Please remember we are not able to respond to questions about specific submissions that might be under review. We will not hold a town hall on Wednesday, July 21. We will resume Wednesday, July 28.

Tim: Thank you for joining, everyone. We are doing this with a different format so hopefully this works. Hopefully there will not be technical glitches. It is quite different from what we have done before, but we will work through those together. Of course, this is being recorded, so if you do not want to be recorded please drop off. First, I wanted to note unfortunately we're seeing a resurgence in cases of COVID in the U.S. We are now daily above 20,000 new cases and we also see many localities experiencing not only high numbers of cases but also high test positivity rates. Many are above 15% positivity. This is unfortunate. It is what it is. We will continue to work hard to deal with this ongoing pandemic. It does for developers, though ease some of the challenges in getting positive samples. In the recent weeks we have expressed willingness, as numbers were falling to have foreign studies done in order to get positive samples, especially in the point of care and home situations and of course we always said we would like to see, we recommend you attempt to try those studies in the U.S.U.S. first

and only if you are unable to get the positives that are needed to go to the ex-U.S. site. We have given a lot of parameters around that. One of the reasons for starting in the U.S. has been we wanted to see even negative sample usability and user interaction in typical point-of-care and typical home situations in the U.S., in English, so we have a good understanding of that. Of course, with point-of-care tests, the U.S. is different than some other countries in how point of care testing is done during this pandemic in a lot of different ways now that point of care testing can be done at schools and at workplaces which have never done it before. There is more than 30,000 new waived labs in the U.S. Traditionally, and we like to see that here in the U.S., that the point-of-care study is done in busy clinical office practices where they are frequently distracted by the many things that they do in that office. And even in the midst of those distractions can get an accurate result. That is the real situation in the U.S. typically for point-of-care tests and we want to make sure the instructions in these will work such that even in the busy setting where they are not just potentially standing there watching the test develop, but if it is 15 minute incubation, they are off doing other things and they correctly get back to the testing workstation, for example, and read the test. Just some thoughts to start us off. With that, Toby I think we can go into the questions that we received prior to the call, and then we will move into live questions. Over to you Toby.

Toby: Thanks Tim . Thanks for joining us, as usual. As we have been for the past few weeks, we will go through some questions we received by email ahead of time. As we've noted before, we have received some questions that are a little bit too detailed or case specific to address on the call. For those questions, we will try to send a response in writing within a few days. And If you submitted a question and don't hear it addressed please look for a written response. If you don't receive one within a few days, please feel free to reach back out to the CDRH EUA Templates mailbox for an update and note that that is CDRH-EUA-Templates@fda.hhs.gov which is a different mailbox than where you submitted the questions

for the town hall. The first question that we have is regarding development of a COVID-19 double amplification ELISA test kit noting that they will be supplying all of the reagents necessary for the assay but that the test results must be read using a plate reader. And they intend to evaluate the performance of the assay with two different types of plate readers. But they are asking that given that the spectrophotometer and plate reader is a common laboratory instrument functioning under a common set of standards and controls, they are asking whether the EUA would require that all laboratories have the same device or model used in the performance studies or whether they can document the specifications and operating parameters needed for the spectrophotometers and to state both how the specifications and parameters were defined and described to the users in the labeling. So we can confirm that that approach is correct for an EUA request for common laboratory instruments such as a spectrophotometer there is no requirement that all laboratories need to use the same brand or model. The specifications and operating parameters applicable to the assay and used in the validation studies should be described for the end-users.

Tim: Okay. Thanks Toby. I think we can go on to the next question.

Toby: Great. The next question is concerning a paper that the inquirer sent along with the inquiry about positive individuals circulating in communities and the implications for symptomatic versus asymptomatic. They note that the paper provides evidence that the viral load for symptomatic versus asymptomatic individuals are equivalent and asking about the FDA's recommendation for additional testing to add asymptomatic claims. So, we want to thank this individual for sending in this paper. We do regularly consider the totality of scientific evidence when we are reviewing EUA tests. We do have additional recommendations for adding asymptomatic claims to tests. But we also have put out, for a couple months ago now, the supplemental template that provides a pathway to add asymptomatic claims prior to validation with that patient population. Tim, did you want to discuss this topic as well?

Tim: Yes. We are very interested in having asymptomatic claims added to tests. We appreciate the reference. We read widely as well for publications we see. It never hurts to forward things to us. We have clearly seen for some studies, for many studies in fact, where there is a difference between the levels of virus and actual performance of tests between symptomatic and asymptomatic individuals. We continue to make decisions for asymptomatic based on data. With that said, for specific devices, with that said though we created some very straightforward pathways to asymptomatic screening. The easiest one is to add a serial testing claim if performance is adequate for the test validation on symptomatic individuals and our guidance there. We are still very interested in making asymptomatic screening claims available to developers and therefore users. Back over to you, Toby.

Toby: Thank you, Tim. Our next question is about the recent EUA for the first fully quantitative serology test. In that authorization, in the press for it, it is noted that quantitative serology tests that are traceable to a certified reference material may be helpful for ongoing medical research to study the immune response to SARS-CoV-2. This question is asking if we could clarify which material would be acceptable for standardization. Generally, we would suggest that you refer to the ISO 17511 standard, and that is the international organization for standardization, ISO, and the standard is titled *In Vitro Diagnostic Medical Devices, requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples* (2019). We would recommend that you use a certified reference material that meets internationally accepted quality requirements that provides a common metrological reference and that has a measurement uncertainty that has been completely established. Tim, do you want to talk further about that one?

Tim: That is good. We can go to the next question.

Toby: Alright. Our next one is about test result recording for molecular at home tests via software or mobile applications. They are asking whether the IVD test developer if, they

want to know if all the test results both positive and negative are required to report to the CDC or healthcare provider automatically and if it would be acceptable for software applications or mobile applications or websites to provide at home users the option to report or not report and whether FDA requires at-home users to report both positive and negative results via software app to the CDC or healthcare provider or if it is acceptable to report only positive results. So we have discussed this previously on this call a little bit that we do not have a requirement for a reporting feature at the time of authorization of an at-home test. We do think that reporting is important and we have asked in some cases for a post-authorization commitment to develop the reporting feature. It is acceptable to have an opt out feature for those who do not wish to report their results.

Tim: The opt out feature is for home-based users who for whatever reason may not want their results reported. That is acceptable. Of course, we want to encourage everyone who uses the device to report results so that we can better track this pandemic. Alright Toby I think we can go on to the next question.

Toby: Thank you. The next question is about the point-of-care claim for an antigen-based lateral flow test. They are planning on using two clinical sites, one in the U.S. and one in India planning on the testing of contrived samples using five to six operators of the U.S. site only and asking whether this testing would support a point of care claim for clinical contrived sample testing. We do recommend the use of actual patient samples, preferably all fresh, for point-of-care. While as Tim mentioned earlier, we do recommend you start with a U.S. based point-of-care study and then only if 30 positives are not obtained in a reasonable timeframe would a non-U.S. site come into play. As Tim mentioned in his introduction, unfortunately cases are surging in the U.S. and there are many localities that have high positivity rates that would be appropriate for performing this testing. And then this same inquiry included a second question about in India the Indian Council of medical research has an approved list of high-

sensitivity RT-PCR assays all with validation studies asking if they could use one of those ICMR approved assays if they supply documentation showing the validation studies and performance of the test. We do ask that all samples being studied with the point-of-care device should also be tested with an FDA authorized SARS-CoV-2 molecular assay. And that the comparator method be one of the more sensitive EUAs on the FDA website. Ideally the same comparator would be used for all samples.

Tim: Sounds good. I think we can go to the next question.

Toby: Alright. The next question is wanting to ensure that their users are appropriate for the claim for the antigen test and asking who qualifies as healthcare personnel, specifically noting that in India a phlebotomist generally conducts the nasal swab and asking whether they would qualify as a healthcare personnel. As we were just discussing, we do recommend that point of care studies be performed in the U.S.. As Tim was discussing earlier, point-of-care settings in the U.S. have a lot of unique features, including both the personnel as well as the setting itself. the U.S. clinics are busy and the point-of-care studies are intended to look at the ability to obtain accurate results in that specific point-of-care setting with all the distractions that are normally taking place in that setting. We would recommend that you consider that and use a U.S. site for your clinical studies.

Tim: Okay. I think we are getting there. I think that ends the last question.

Toby: Yes.

Tim: So I think we can move to questions. It looks like we have folks that have already raised their hand. We will go in order of when the hands were raised. It looks like there is more coming on now. We look forward to that.

Kevin Flinn (AV Support): The first question comes from Fiona Wang.

Fiona Wang: Hello. My question is about neutralizing antibody. I submitted a pre-EUA of my PRNT protocol to FDA but I haven't heard anything from FDA yet. If I haven't heard from FDA, can I assume that FDA accepts the PRNT result from any lab?

Tim: So, you know, we are still getting up to 200 new applications a month, including original pre-EUAs, original EUAs, supplements and amendments. We are post surge capacity. So we are back down to where we were before the surge. We are struggling to get through all of it. We have laid out for neutralizing antibodies a pretty good recommendation. You are welcome to go ahead on risk to that. You can also follow up with maybe extremely targeted questions perhaps through the template email address asking it be sent to the reviewer that has been assigned to your pre-EUA. It does not imply unfortunately that we agree with all of the plans.

Fiona Wang: Okay. Yeah because PRNT is a very long and expensive process. It takes about seven weeks so I just wanted to do it right at the beginning. That is the reason I submitted the pre-EUA .

Tim: So I think just sending an email to the templates email address with those very specific questions that hopefully it can be addressed relatively quickly.

Fiona Wang: Alright. Thank you so much.

Kevin Flinn (AV Support): Next question comes from E Rozen.

E Rozen: Good afternoon. My question is also regarding serology tests for neutralizing antibodies. On the March 17 template it is suggested that we only utilize one or two collection sites. I was wondering a. what the rationale is for the decision and b. if in an effort to increase enrollment FDA would accept enrollment at more than two collection sites for this sort of trial.

Tim: Toby, you may know, but typically we list the more minimum number that we like to see. I think more sites should be fine. I don’t know a reason why more wouldn’t be okay.

Sometimes we want to see more than 1 site. And I am guessing that is more than likely the reason for the language. So it is more of a minimum number than a maximum number.

E Rozen: Alright, great. If you do not mind, I have one other quick question. We have conflicting information about whether vaccinated individuals be eligible for enrollment in a serology trial looking at neutralizing antibodies. Just wondering if you could shed more light on that question and what FDA would be considering as appropriate for enrollment for this sort of trial.

Tim: We would recommend for neutralizing antibody serology assays at this time to use those that were naturally infected.

E Rozen: Understood. Thank you very much.

Toby: And just to jump in on the first question about the collection sites more than two is okay. That was more of a minimum.

Kevin Flinn (AV Support): The next question comes from Michael Patz.

Michael Patz: Hello Dr. Stenzel. If you could go back and repeat your comment about opting out of reporting for the OTC tests. I missed the very beginning of it.

Tim: Sure. Opting out in the reporting feature just to go over that whole topic again, for home testing, whether its OTC or prescription home test, we would like to see reporting functions included. We will authorize the test without such. It is not a requirement at authorization. We do ask that the developers commit, if they do not have a reporting feature when we authorize that they develop one. There are a number of different potential partners and we have folks internal to the office who can assist you in linking you or anyone else up with a reporting developer. It is not a requirement for authorization. It's a commitment we have asked in the home situation whether it is home OTC or RX that the opt out feature is that an individual at home can turn off the reporting feature so that their data isn't shared through the app wherever it would go. We would recommend that that be a manual decision by the user to

opt out basically everyone is signed in unless they opt out so that we get the maximum number of reports and we can better track what's going on with this pandemic for home users that authorize the reporting of their data.

Michael Patz: And if I could just ask to get connected with those developers at FDA how should I go about doing that?

Tim: You should send an email to the templates email address and ask to be connected with Dr. Sara Brenner. She and her team can work with you. She is heading up a reporting and software group for testing for SARS, among the many other things she is doing. Thank you.

Michael Patz: Thank you.

Kevin Flinn (AV Support): Next question comes from Dave Rabiger.

Dave Rabiger: Hi. There is a lot of information and options regarding pursuing pooling claims for upper respiratory samples. Has FDA considered or is there any guidance for the manufacturers of molecular tests who wish to pursue a saliva pooling claim?

Tim: Recommendations for saliva pooling? I do not think we have specific recommendations for that, but we are open to it. It may be more difficult a say in point-of-care setting or in a home setting, but absolutely open to it and would pretty much follow what we are recommending for swabs. You can pool the saliva first and then run your assay and determine with the various methods that we recommend how many samples you can pool and not reduce the potential sensitivity too much. We would like to see that the sensitivity doesn't drop below an overall 85% relative to the saliva run straight on the same device. There is a pooling amendment or pathway to add pooling more easily. That option is not available for saliva. That is only available for nasal swabs. That does not mean we are not open to the submission for pooling of saliva. Hopefully that addresses your question.

Toby: We have authorized at least one test for pooled saliva samples. If you search for saliva on the EUA table, you should be able to find that and you may want to take a look at their authorization to see if there's anything that would be helpful for you.

Dave Rabiger: Thanks Toby.

Kevin Flinn (AV Support): Next question comes from Mike Wang.

Mike Wang: Hello. Thank you for taking my question . My question is about the robustness studies for point-of-care tests. So we have a semi quantitative point-of-care antibody test. In the template it says that for the specimen volume we should be testing in cases where specimens are provided at half the amount and also double the amount of the indicated amount. And so since our test is semi quantitative, if you provide half of the amount, the way it works is it's a test that takes in a fingerstick whole blood and if you provide half of the amount of blood, then the results will show half the amount of antibodies and if you provide double the amount of blood it will show double the antibodies. So is that not acceptable for a point-of-care use case?

Tim: Yeah. That is exactly why we asked for the flex study. These flex studies, or robustness studies, are designed to test non-laboratory healthcare workers and their ability to perform tests. They are not trained in precision pipetting. The ideal device, as you describe,would recognize the volume is not sufficient or it is too much. It would not provide a result or would provide some feedback. So as your device is designed right now, it might be more appropriate for a moderate or high complexity situation. I would have this specific dialog with our review staff and what mitigations you might have for this. But typically, providing precision pipetting or precision capillary blood assessment in the point of care setting is more than the traditional say settings of being skilled at. There is enough concern about untrained laboratorians performing tests and we try to make it as easy as possible for them. Many of them just follow pictures. That is the intent of the flex studies. That could be a review issue for us.

If you still want to pursue that I recommend having this specific dialogue with our review staff as soon as possible.

Mike: I understand. Thank you.

Operator: The next question comes from Kelly.

Kelly: Hello. Thank you for taking my call. Working from the October 26 antigen template and working on a multi-analyte respiratory point of care test. We need to establish performance using retrospective samples and therefore trying to understand how FDA defines low viral load samples for the respiratory panel. As discussed in a prior Town Hall on June 16 we understood that we needed 20-25% of the sample with the low viral load plus/minus 3CT of a comparator device. For us to better understand how you are really characterizing this, does that mean that hypothetically, and this is just completely hypothetical, for a point of antigen test if you have an analytical LOD that is equivalent to say a CT of 30 on a cleared or EUA authorized influenza test, influenza PCR assay, would that mean you are looking for 20- 25% of your samples to be greater than a CT value of 27?

Tim: I do not believe that recommendation is currently in our template. It would be ideal to see low non-SARS viruses but for now it would be a recommendation and not a requirement to do that. Typically for low positives the comparator device would be three CTs above and 3 CTs below the stated LOD of the EUA authorized device. Toby, anything else to add on to that? Hopefully that addresses your question.

Kelly: It kind of addresses it. So it's plus/minus 3CT of the comparator device and not your device as it compares to the EUA authorized device. So if an LOD is, for example, my understanding of the influenza test is that anything below a CT of 42 is considered influenza positive on a PCR device, so if the cutoff is 35 then you are looking for 32 to 38 on the comparator device as your low viral load. I am trying to understand really that comparator device.

Tim: Yeah. So cut off and LOD can be different. And we are really looking at, and typically the cut off is lower than the higher CT. For devices that are specific enough, have a high enough NPA. We are not asking for samples that are below the cutoff of the comparator device but a lower CT than that so plus/minus. So, If you said the cut off was 35 you said?

Kelly: For example. I just was taking that as an example. On your PCR your comparator has 35 or below was considered positive for this specific comparator then you are looking for 32 to 38.

Tim: Again, it is the LOD so if the LOD is at 35 cycles on the device. Then we would say for the LOD that 32-38 would be the range for the low positives.

Kelly: So for clarification, one more time, let me go back. I'm a little confused here. So the LOD of My comparator then, because what I am trying to understand if my analytical - obviously my analytical LOD will not be the same as my PCR LOD for an antigen test. So for an antigen test, I was trying to understand are you talking about the analytical LOD as the equivalent CT value on the PCR device?

Tim: Yes. It is the PCR device that defines whether it is high or low. That's the authorized device so the FDA has authorized it so that's what we're going with. It is the closest thing to truth that we have.

Kelly: Also I do not find that an NPA is ever a requirement for NPA the only requirement I find is in the template for manufacturers of molecular and antigen diagnostic devices for non-laboratory use and there it's an NPA of greater than or equal to 99% with a lower bound confidence limit of greater than 95%. Does that also apply for the regular antigen template?

Tim: For point-of-care antigen that I think is for OTC. With OTC you don't have a health professional involved at all and interpreting results and there can be a false positive with any device. It was a recommendation that OTC devices have a very high specificity of NPA.

You can look at what we have authorized to see what has been able to be achieved we do not typically recommend an NPA at this time because in some situations there's a little bit more flexibility between devices, we do not want to set up a recommended level for all devices. We know rapid antigen tests have a slightly lower NPA than a good central lab molecular test but that they both have false positives. We are not expecting perfection in the clinical studies. There are few devices that are perfect. We are aiming for as specific a device as possible. Definitely in serology and more frequently than other devices have seen issues with specificity or NPA being too low and an antigen test, for example, or a point-of-care that's too low you are going to end up generating a lot of false positives, and there is risk of a false positive and there is harm. We have had MDR reports of that harm or potential harm. Sometimes healthcare workers put those positive patients without confirmation into the COVID ward. That puts those patients at increased risk of actually acquiring COVID. Hopefully that helps.

Kelly: Okay. Yes it does. Thank you.

Kevin Flinn (AV Support): The next question comes from Tingyang Liu

Tingyang Liu: Hello. Thank you very much. Here is a question. If one OTC product has a very high NPA rate and sensitivity rate, that means the accuracy is good. Could the OTC products be used as POC or operated by professionals?

Tim: Yes. If a test validated per the OTC recommendation and is authorized over-the-counter, it automatically comes with the ability to do it in a clear way setting. A separate study is not needed for point-of-care use. It is more challenging to show ha device works in the home environment than it is with the healthcare workers doing it in a clinic. It is a little bit of a higher bar. If you can achieve that and get that authorization, it can be used in any of the lab settings. It is a more efficient route to go to go the home route initially, if that is what you really want to get to and if you're confident in your risk in your development program is relatively low to

go directly to OTC, then it is more efficient. You do not do two separate clinical studies. It is just one.

Tianyang Liu: Okay thank you very much.

Toby: And I would just add for that the only thing that you may want to consider is whether the instructions for use need to be modified for the point-of-care setting so that the operators of the CLIA waived point-of-care setting will be able to follow the instructions for use directly purchase things like that. If it is intended to be used at the point-of-care, you want to make sure that there is an option in the instructions for the point of care operator to perform the test whereas if the instructions just say test yourself that may cause some problems.

Okay. Thank you. In this case, if we got the OTC approval for the original product, then if we want to use for POC then we would need to adjust to the instructions of use. Does it need to go through to the application again.

Toby: We would work with you on that during the review.

Tim: Yeah, and if it is already authorized for home OTC use, it is us reviewing the labeling I read instructions for point-of-care.

Tianyang Liu: Okay. Got it. Thank you very much.

Kevin Flinn (AV Support): There are no more questions. Back to you.

Irene: Thank you, this is Irene Aihie, and we appreciate your participation and thoughtful questions during today's town hall. The transcript will be made available on the CDRH learn webpage at www.FDA.gov/training/CDRHlearn by Wednesday, July 21. If you have additional questions about today's presentation, please email CDRH-EUA-

Templates@fda.hhs.gov. Again, we will not hold a town hall on Wednesday, July 2st we will resume Wednesday, July 28. We would appreciate your feedback.

Irene: Following the conclusion of the virtual town hall, please complete a short survey about your FDA virtual town hall experience. This survey can be found now on www.FDA.gov/CDRHWebinar. Again, thank you for participating. This concludes the town hall. You may now disconnect.

[Event concluded]