FDA Virtual Townhall

Moderator: Irene Aihie
May 26, 2021
11:15 pm ET

Coordinator: Welcome and thank you for standing by. At this time, all participants are in a listen-only mode. At the end of today's presentation, we will conduct a question-and-answer session. To ask a question please press Star 1. Today's conference is being recorded. If you have any objections, you may disconnect at this time. I would now like to turn the meeting over to Irene Aihie. You may begin.

Irene Aihie: Thank you. Hello. I'm Irene Aihie of CDRH's Office of Communication and Education. Welcome to the FDA's 57th in a series of virtual Town Hall meetings to help answer technical questions about the development and validation of tests for SARS-CoV-2 during the Public Health Emergency.

Today, Toby Lowe, Associate director of the Office of In vitro Diagnostics and Radiological Health and Dr. Timothy Stenzel, Director of the Office of In vitro Diagnostics and Radiological Health in the Office of Product Evaluation and Quality, both from CDRH, will provide a brief update.

Following opening remarks, we will open the line for your questions related to development and validation of tests for SARS-CoV-2. Please remember that

during this Town Hall we are not able to respond to questions about specific submissions that might be under review. Now, I give you Toby.

Toby Lowe: Thanks Irene and thanks everyone for joining us yet again this week. I don't have any particular announcements today, so I'll start with the questions that we received by email ahead of time. The first one that we have is related to equivocal evaluation study preparing for a 510(k) submission for a respiratory PCI multiplex panel, including COVID-19 Flue A-B and RSV. The question notes that FDA generally requires that the Flu and RSV comparative methods be cleared by 510(k) PCR devices. But they're getting feedback from many CLIA labs that manufacturers have stopped selling their Flu and RSV multiplex kits and are only manufacturing their EUA multiplex kits that have COVID added into it.

So, the question is asking whether it would be possible to use an EUA respiratory multiplex kit for COVID, Influenza, and RSVP, I'm sorry, RSV as the comparator in the clinical study. So, generally we do recommend that the respiratory multiplex comparator methods are 510(k) cleared. But we do know that that's, that maybe challenging at the moment, so you could also consider using an EUA-authorized, highly sensitive RT PCR assay as your comparator method for your clinical evaluation.

But we do note that the EUA tests are validated with a different level of evidence than a 510(k) tests, a cleared test. So, we would probably recommend that you use multiple EUA tests in an algorithm to determine positive and negative comparator test results.

For example, you could use two EUA tests per sample of the comparator and if there's disagreement between those, use a third tiebreaker test. And as we've mentioned here on this call before, we do recommend that if you're

pursing 510(k) pathway, that you submit a presubmission to discuss your proposed comparator method. And, you know, as I'm sure most of you are aware when you submit your 510(k), you do need to have a predicate that has been cleared or Denovo-granted device. And so, right now that is just the BioFire assay so that would be an appropriate predicate, but it does not have to necessarily be your comparator method.

Our next question has to do with a topic that was previously discussed on the Town Hall, where the question is stating the FDA mentioned that after 50% of clinical specimens for a 510(k) clinical validation study can be frozen prospective specimens. And they're asking if we can confirm if frozen retrospective samples can be used as well if they're retested on a comparative method in the clinical study.

And if not, to please provide more information on how the frozen prospective samples should be collected to qualify for the clinical validation study. Such as whether they can be US or outside the USA, if they must be collected during the clinical validation study and not before; whether the concerned positive-negative status must be known.

So, generally we do recommend that clinical studies include prospectively fresh and frozen samples to preserve analyte prevalence. Retrospective samples are considered to be selected and archived samples that are previously frozen usually based on a previous positive result.

So, since that approach is more than minimally biased since the prevalence is generally not preserved, that's not, not our recommended method. Typically, the, or often the archived samples are also very high concentration so they would not be near the LOD of the assay and may not be reflective of the actual patient population. So, we do agree that sponsors can supplement with

retrospective samples but usually only after conducting a prospective study which yielded too few samples to demonstrate adequate performance.

In terms of US versus outside the US, we recommend that sponsors conduct their prospective clinical studies primarily in the US to support a 510(k) or Denovo. Data from outside the US prospective clinical studies can also be submitted to supplement the US data, especially in cases where there's difficulty getting enough specimens in the US due to low prevalence with a heavily vaccinated population.

Our next question also has to do with enrichment studies due to the current COVID positive cases decreasing here in the US. And mentioning a comment in that Dr. Stenzel made on a previous Town Hall about the acceptability of enriching studies in order to meet the study requirements. The question is asking if we can clarify what would be appropriate for study enrichment. So, there are multiple options for clinical study enrichment, and they really should be appropriately tailored for your specific test and the claims that you are validating. So, we do recommend that we, that you submit a pre-EUA so that we can review your proposal and consider the alternate study designs that would streamline enrollment of positive subjects when prevalence drops low. That would be best appropriate or most appropriate for your, for your situation.

Dr. Timothy Stenzel: Yes, and thanks, Toby. And I would add that, the original reason to offer enrichment was for stimulating additional development of screening assays. You know for screening asymptomatic patients and when it was, when in sometimes in populations that's very low or you have to screen a lot of folks. We have now considered doing to allow enrichment for original submissions where obtaining of positives may be more challenging, symptomatic positives even. And, you know, where maybe banked samples are not appropriate or of

such. But we would still like to see, you know, a prospective attempt to try to get true positives and then looking at supplementing them with a method of enrichment. Banked samples is one.

The other is to use some sort of selection where a patient may be and this might be more, so for, an asymptomatic carrier then an symptomatic person. But it could also be done with an symptomatic person and that is, where they are identified as positive with some orthogonal method and some sort of routine study or protocol for screening. They would be open to study designs that try to mitigate the bias in that situation. If the patient themselves knows the result of the test and it's not going to involve self-collection for the candidate test, then that may be acceptable. If the patient although is going to be doing self-testing with candidate device knowing the previous result, this will bias the result.

But, you know, for the situation where they're not going to be self-collecting for the candidate device, the person doing the collection, you know, should be blinded to the previous results. The patient should be asked not to identify whether they were positive negative and of course, to keep the immigration of the study honest and unbiased. A suitable number of negative patients should be offered in the same way so that the person doing the testing doesn't assume that it should be positive. This way, bias can be mitigated to a greater extent. So, there are multiple paths, and we're open to multiple paths.

We do recommend, highly recommend, that you run those strategies by the FDA prior to initiating your study. And in order to avoid any sort of duplication of studies because study plan and design was not suitable. Back over to you, Toby.

Toby Lowe: Thanks Tim. That's really helpful, that additional information. Our next question is regarding a professional use, rapid antigen test. This sponsor is conducting a clinical study and has so far collected some positive samples but none of them have CT values over 30. They're looking for FDA feedback on what to do if they're still not able to get any or enough low positives since FDA generally does want to see 10 to 20% of positive samples being low positives with a CT over 30 for antigen tests.

So, we do, generally, we still need to see at least 10 to 20% of low positives as observed in other sequentially collected prospective studies. But we, we are happy to discuss enrichment strategies that we just talked about in a pre-EUA. So, we would request that you a pre-EUA with your proposal and we can give comprehensive feedback that way.

The next question…

Dr. Timothy Stenzel: So.

Toby Lowe: Oh, go ahead Tim.

Dr. Timothy Stenzel: If I could add just a little bit to that.

Toby Lowe: Yes.

Dr. Timothy Stenzel: One thing with an antigen test device, if you're skewing patients towards the early days of symptoms, that may have an effect on comparator CT values. We would expect it to be higher once the PCR test is positive. So, we look at the scatter of patients across the window of claimed days of sensitivity and that may be that collecting more samples further out from symptoms in the study is a way to enrich. But if you're in the situation, we do recommend you

come in with a pre-EUA and discuss your challenge and potential solutions with the FDA team. Thanks. Back over to you, Toby.

Toby Lowe: Thanks Tim. So, the next half of this question is about, for the same rapid antigen test, asking about usability in clinical studies for non-prescription, over the counter use. The question notes that a couple of products were recently granted EUA for over-the-counter serial testing so they're asking questions about whether the usability study and the clinical study need to consider serial testing in the study protocols design.

So, I want to make sure that everyone, including the sponsor, is aware of the supplemental template for adding serial testing. That was put out in March, I believe, and it does lay out exactly what situations we think we can add serial testing including over the counter serial screening, without having prospectively collected data on asymptomatic individuals or for serial testing specifically. So, for the initial authorization we would not expect to see serial testing specifically evaluated in your usability or clinical study.

We would expect you to follow that, you know, the antigen template and then that supplemental template which indicates that you would need to demonstrate a PPA of 80% with a lower bound of 70% for individual single-use testing on symptomatic individuals. And based on that performance, we would be able to give you the indication of serial testing for asymptomatic individuals with a post-authorization requirement to validate the asymptomatic serial testing claim. And that would be through a protocol that we would review interactively with you before you implemented that as your post-authorization requirement.

All right. I think we have another question. Oh, go ahead.

Dr. Timothy Stenzel: Yes. What is the next question? Do you want to just read the next question as I may be answering one of these that are coming? It would be the EUA letters of authorization question that's next.

Toby Lowe: Yes. There is a question about EUA letters of authorization containing several statements that are required to be included on all descriptive printed matter, advertising and promotional materials. And the question is asking for online advertisements, is it acceptable to omit the statements due to space limitations if a link to a webpage with the full list of statements is included in the online advertisement?

Dr. Timothy Stenzel: Yes. Toby, I didn't see a prepared answer so I will jump in unless you have this one?

Toby Lowe: I think we were planning to get a written response for that one to make sure we get all of the legal nuances on that one actually.

Dr. Timothy Stenzel: Oh, yes. Okay. Well, my suggestion was going to be that, you know, that is in the letters of authorization. We generally expect that to be followed but if there is some sort of situation or that's hard, we're open to different ways of handing it. So, I would approach the FDA on that but typically we want all the important information on all of the materials. Thanks Toby.

Toby Lowe: Yes. Great.

Dr. Timothy Stenzel: Back over to you.

Toby Lowe: Thank you. All right. Let's see. The next question is about a 510(k) for our molecular SARS-CoV-2 RT PCR with claims for asymptomatic population and asking FDA's thoughts on comparator method for, for that study.

Specifically, whether the comparator assay needs to have asymptomatic claims and whether the comparator assay needs to be cleared. And as well as whether the BioFire RP-2.1 assay is an acceptable comparator. So, we have not, we don't currently have any tests that are cleared with an asymptomatic claim for SARS-CoV-2 So, at this time we would recommend that you use a comparator method consisting of two EUA-authorized, highly sensitive RT PCR assays that do have that asymptomatic claim with a third test available as a tiebreaker. And as we've discussed previously, we do recommend that you submit a pre-submission to discuss your individual comparator method prior to moving forward with that towards the 510(k).

And our next question is about clinical evaluation of a point of care or over the counter antigen test for an EUA. Asking about due to the declining number of positive in the US, whether some or all of the study can be completed outside of the US? So, we do, it is acceptable for some of the data to come from prospective clinical studies outside the US to supplement a US-based prospective study. If that US data is not sufficient due to low prevalence in the US simple due to a heavily vaccinated population now.

However, we would need to understand if the testing is being conducted under the exact same protocols and whether the population tested appropriately represent the US population. So, we would recommend in that situation to submit a pre-EUA to discuss the proposed clinical evaluation to make sure that it is appropriately designed and carried out and we can give comprehensive feedback to you that way.

Our next question is for, there's two questions. One about an antibody test, asking whether a prospective study is required for antibody, Denovo, or 510(k) submissions? Or whether a retrospective study can include some samples from outside the US? So, we do recommend that sponsors conduct

prospective clinical studies primarily in the US to support a 510(k) or Denovo. Again, similar to the previous question, data from outside the US prospective clinical studies can be submitted to supplement the US prospective data. And if collection sites outside of the US are chosen, you should document the relevance of the studies to the US clinical practice and demographics.

And the then second part of that question is about an antigen test, Denovo, 510(k) submission when only claiming use with nasal swabs whether the comparator method can be a high sensitivity RT PCR with nasal swabs? Or does it need to be an NP swab for the comparator? So, we do, we do. We have been accepting nasal and mid-turbinate swabs for the comparator method for EUA submissions and I would expect we would do the same for a Denovo or 510(k). But we do recommend that you submit a pre-submission again to discuss that study design so that we can provide comprehensive feedback.

Dr. Timothy Stenzel: In one sample type, Toby, that doesn't follow that recommendation is saliva where we still recommend a NP swab. But for saliva, we'll also entertain a mid-turbinate swab.

Toby Lowe: Great. Thanks. All right. Speaking of saliva, our next question is about, is about saliva noting that on previous Town Halls, we've mentioned that saliva is a challenging sample type for antigen tests. And asking whether we could explain more details on what issues were uncovered. I do want to note that we have mentioned that saliva is a challenging sample type, both for molecular and antigen tests, not just antigen. And then the other question also notes that FDA mentioned that freeze-thaw processes increase sensitivity in saliva antigen tests and asking if this is the case for antigen testes detecting the N protein or the S protein or both.

So, we have seen that saliva is a challenging specimen type. Detection from saliva is typically less sensitive than upper respiratory specimens. The freeze-thaw issues can affect the samples in different ways and in some cases we've seen where it increases and in other cases, decreases. And so, we have seen some variability in the data that we've seen from test developers with saliva in terms of the ability to appropriately validate it and to get appropriate performance with saliva. Tim, did you want to add anything?

Dr. Timothy Stenzel: I would add that…

Toby Lowe: More? Yes.

Dr. Timothy Stenzel: Yes. I would add that the freeze-thaw cycle, we recommend it be investigated if you're going to use frozen samples for any EUA authorization to show that there is no bias in using frozen samples. Okay. Thanks. Back over to you.

Toby Lowe: Great. And then the last prepared question that we have is about submitting an EUA for a point of care molecular diagnostic test system with an optional app to communicate the results of the test to the appropriate authorities if the user desires. Asking whether it is a requirement to include validation data for the optional app as part of the initial EUA submission. Or if use of the app could be filed separately or whether or not it is even necessary to provide validation data for the optional app.

So, for that it would depend a little bit on the role of the app and how it interacts with the test itself. So, that's something that we would likely want to have a more in-depth conversation with you about. So that we can better understand the interaction between the test and the app before we provide that feedback, and I would submit a a pre-EUA anyway. Sorry, go ahead, Tim.

Dr. Timothy Stenzel: I just wanted to wait until you're done. Are you done?

Toby Lowe: Yes. Go ahead.

Dr. Timothy Stenzel: Okay. I just wanted to say that's my fault, we passed over on one of the questions earlier and I wanted to go back and answer it. And the question had to do with when does the FDA anticipate a recommended reference material is available for antigen tests. And at this time, we don't have such a recommendation or a panel. There are clear challenges in doing this for antigen tests and currently we do not have anything stood up. You know that'd be great so we're obviously thinking about it but nothing right now. Thanks, and Toby, I think that might be the end, and can we go to the open line for questions?

Toby Lowe: Yes.

Dr. Timothy Stenzel: Okay. Back to you, Coordinator:

Coordinator: Thank you and at this time if you would like to ask a question, please press Star 1. Please unmute your phone and record your first and last name clearly when prompted. Your name is required to introduce your question. To withdraw your question, you may press Star 2. Once again at this time if you would like to ask a question, please press Star 1 and our first question is from Alex. Your line is open.

Alex: Hi. This is Alex with UserWise Consulting. We specialize in human factors and usability testing. My question is about inclusivity testing. Is there any expectation that manufacturers of OTC antigen tests include new recent strains of the virus in inclusivity testing? Or they can rely on very common

strains sourced from Europe, for example? And can you generally explain your latest expectations on the quantity of strains and which strains should be used for inclusivity testing?

Dr. Timothy Stenzel: Yes. Toby, you can correct if I'm incorrect on the guidance related to variants and mutations. Our intention there was for developers to take a look at the variants in the US population when they do their validation tests and determine whether or not there might be an issue with certain variants. If, you know, by informatics analysis, you know, you see where the mutations are, you know how your, you know what antigen your antibodies were raised against. So, you know at least that the area of the virus that you should look for potential, you know, issues with certain mutations and variants.

And apparently, with one of the antigen tests there's has been, fortunately, in low abundance a mutation in the United States but we don't expect it to increase. But it has been in studies shown to not detect a particular, a particular mutation, virus with a peak of mutation. So, this has been proven to be real already from molecular and now it's proven to be real for antigen.

Serology may be a little bit more insensitive to mutations and variants due to the polyclonal nature of immune responses. And that may help since there would certainly be a clear example that come up in serology as well.

So, we are currently surveying for tests on the market, molecular, antigen, and serology. The information that we received from the developers having to do with how their tests were designed allows us to do a first pass, at least for antigen, and serology tests for potential issues with inclusivity. You know, and false negatives and we are currently reaching out when we have a potential concern in engaging those developers. And it is important for those

developers to get their hands on some sort of protein molecule with those variants.

We're open to a different, on what methods to do that. I would suggest that if you do determine that there could be false negatives with overall at or above the 5% mark in the US population. Or a single variant or mutation that's at or above 5%, that you engage with the FDA on your strategy to assess that pre-authorization. So, that we have good assurance that it's not going to affect performance of the assay.

We also have in that guidance asked that you come in when you're coming in with your EUA, that you come in with a plan for how you're going to, on an ongoing basis, assess the risk of false negatives due to variants and mutations. And we'll look to that and get feedback on that because that will be a post-market commitment that we will require for developers to monitor that situation. Toby, anything to add?

Toby Lowe: Yes. That's, just in addition to what you were covering, I would also note that the EUA templates do include recommendations for inclusivity testing. So, I would also suggest that you take a look at the template for the specific type of test that you're looking at.

Alex: Thank you.

Coordinator: Thank you. Our next question is from Shannon Clark. Your line is open.

Shannon Clark: Hello. This is Shannon Clark with UserWise Consulting. Thanks for that really helpful response just now. Another question. My understanding that is in order to obtain over the counter designation for an antigen test kit with a mid-turbinate swab. That requires the inclusion of a stopper for child safety to

prevent over insertion. First of all is this true? And then is the purpose of this stopper to prevent gross over insertion such as the stopper could be located four centimeters from tip? Or does it need to prevent insertion past sort of a zone for two-year-old's which is about 1.5 centimeters or a half inch? What is the purpose of that stopper and is it required?

Dr. Timothy Stenzel: It is safety related and we'll take this on a case-by-case basis. For example, we've had some developers come in say, you know, that they're going to require a mid-turbinate swab. And it's sort of in the gray zone just beyond an interior nares, you know, sort of in the, I don't know, one inch or one centimeter, I forget. You know versus a deeper, a true, you know, right up there mid-turbinate swab. But it is a safety consideration so we will take this on a case-by-case basis per the device and per the device instructions. So, if there's any questions or potential concern about that engaging with the FDA early is good prior to doing your user usability studies and perhaps also in your clinical studies to make sure that it's done in a safe manner.

Shannon Clark: Okay. Thanks so much.

Coordinator: Thank you. Our next question is from Jackie Chang. Your line is open.

Jackie Chang: Hey. My question is about the expectation for fully quantitative serology tests and also, and also for a fully quantitative neutralizing test. Right now, the two templates are for semi-quantitative tests and I'm just wondering if, if the validation requirements are just doing everything that is listed for the semi-quantitative test. And then also, establishing traceability of the results to the who sender.

Dr. Timothy Stenzel: Yes. Establishing traceability is important to the National standards for pointing out International units but also, you know, linearity and other issues.

So, I believe we've authorized one truly quantitative test if I'm correct. So, there is some information in that online information about that test, so I'd check that out. We are working in this area, it is an area of importance and focus for the FDA and the serology team. It's neutralizing antibodies and fully quantitating antibody assays are a top priority, high priority, for serology tests. So, if you have, you can submit a pre-EUA and put in there what you think based on the prior authorization and how you want to plan it. And then, you know, we can provide some feedback on the validation study plans and whether our recommendations are more specifically for your device.

Jackie Chang: Thank you.

Toby Lowe: And just to clarify, we have, we've authorized semi-quants. We have not authorized a fully quantitative test yet, but we do, we are happy to help provide feedback through the mailbox or through a pre-EUA.

Jackie Chang: Yes. So, I submitted…

Dr. Timothy Stenzel: Submit a pre-EUA, that's the way to go.

Jackie Chang: I submitted a question to the mailbox, and I haven't received any answer yet, but I really appreciate the answer. Maybe…

Dr. Timothy Stenzel: Send it back through and copy Toby. Ask them to copy Toby and me when they reach out to the team. Because the team has put together their thoughts on fully quantitative and obviously, we've been thinking about it and engaging with sponsors already for me with fully quantitative already. So.

Jackie Chang: Okay. Thank you.

Coordinator: Thank you and as a reminder if you would like to ask a question at this time, please press Star 1. Your next question is from Codimode Vanke. Your line is open.

Codimode Vanke: Good afternoon. Thank you for taking the question. This question is related to the serology tests. I just wanted to find out, I know last year there was an umbrella EUA for serology tests, and then the independent validation was done at NCI. So, my question is, is it, the NCI has done now the validation or is it still the independent validation is in effect? If you could just give me an update. I'd love to hear. Thank you.

Dr. Timothy Stenzel: Yes. The NCI is still open for business as they say for those assays that the FDA prioritizes for the NCI. And we've asked the NCI to stay through a period of time where I'd say they're converted to a full authorization. Or we receive a novel application through either a Denovo or a 510(k) pathway following the first granting of the Denovo application for serology.

Toby Lowe: And if I could clarify about your question about the umbrella EUA. There was an umbrella EUA issues last Spring and last Summer, it was revoked. There were no tests that were, that were added under it, so it did not impact any specific tests. But the umbrella EUA itself was revoked and we have been using the individual EUA pathway instead for serology tests including the ones that have been evaluated by NCI.

Codimonte Vanke: Yes. Thanks. My question was for something similar to what the team answer, is it still the NCI is doing the independent validations. The question is has the backlog of the submitted they have done and then the reports have been given. Or are, are there things that are being done at a different lab?

Dr. Timothy Stenzel: That's a great question. I don't have an answer for that today. I know that, that we constantly look at priorities, and if there is a priority, we do let the NCI know. So, but I don't, I haven't tracked lately what that backlog is. I can't respond directly to that…

Codimonte Vanke: Thank you.

Dr. Timothy Stenzel: …at this time.

Codimonte Vanke: Thanks.

Coordinator: Thank you. Our next question is from Shannon Clark. Your line is open.

Shannon Clark: Oh, hello. Shannon Clark with UserWise Consulting. So, a question about vaccinations. So, obviously you can't run a clinical study for a serological test kit with vaccinated individuals as vaccinations may influence the presence of antibodies. However, can you include vaccinated individuals with an antigen clinical evaluation study?

Dr. Timothy Stenzel: Toby, I believe for antigen, yes. But we would want the data separated out with those who have been vaccinated versus those who haven't. But and the performance could differ and in particular, if someone is vaccinated, they might have lower levels of virus in their nasal passages. And it could potentially impact the performance of the antigen test.

So, we don't, I'm not familiar with any data that we have yet on antigen test performance in vaccinated information. If somebody is doing some research on that out there, we should probably ask our antigen team if they've seen that yet. Because sometimes we keep our nose to the grindstone with the applications but it's a good question. And it's just a word of caution that, that

vaccinated people may not behave the same way on a symptomatic follow up infection as a primary or natural infection.

Shannon Clark: But it doesn't necessarily double our sample size. We can just collect the data and then analyze the data separately if needed?

Dr. Timothy Stenzel: Yes. You may find that it really drops with performance there and we'd like to see the data in the vaccinated population. If it doesn't really drop the performance, we just want to see the data also separately. You may list it separately in, you know, together and separately in the IFU.

Shannon Clark: Okay. Thanks so much.

Coordinator: And at this time, I'm showing no further questions.

Toby Lowe: Thank you.

Dr. Timothy Stenzel: Okay.

Toby Lowe: Oh.

Dr. Timothy Stenzel: We have a little bit of time so we can, we can just wait a minute or two and if there are no further questions, we can give it back to you, Irene, if that's okay. Give it a minute, not too long, but we're available and ready to answer questions.

Coordinator: And as a reminder if you would like to ask a question at this time, please press Star 1. We have a question from Codimode Vanke. Your line is open.

Codimode Vanke: Yes. Thanks for taking the question. My question is for serology tests that just like how NCI is doing, I mean, has been doing, looking for the binding antibodies. At NCI, or are there any other institution that might also do the vaccine antibodies? Do you have any plan about having a center that can do verification validations for antibodies that can show neutrilizing antibodies are protective antibodies?

Dr. Timothy Stenzel: Yes. So, we're, you know, we recently issued a statement on use of serology for vaccinated folks and people that had a natural infection and the implications currently for what can be said about protection or immunity. Which, you know, studies to our knowledge haven't been done to support that use. So, potentially both neutralizing and non-neutralizing assays could be used, mostly likely, through quantitative assays are going to be the assays that are going to provide the most important information about that if things go as we hope. That we it's just the presence or absence of antibody in other examples where, where a test has been authorized to assess the vaccination. But it's the level of antibody sometimes that, that is important. It's an obvious area for us to look into, getting additional information about the serology banked samples at NCI having do with quantification of antibodies and the presence or absence of neutralizing antibodies.

So, it's certainly an area of active discussion right now but in all, because the focus may be more on truly quantitative assays. Those are truly, those are usually not going to care about assays although I'm not going to rule it out. So, it may be something that we eventually design a blinded panel for if we can, you know, depending on how soon we can stand up such a program. But I can't make any promises that one will be stood up and if it is stood up, how long it will take to stand it up. But it's an obvious area for consideration right now.

Codimonte Varte: Thank you. But I think in the past when you were mentioning vaccination is not diagnostic so do they really need the approval the way in which it is done. And, you know, I think it was a positive mention that NCI did a discuss with CBER and we will discuss? And also, can you just mention still it is a part of CBER team, vaccine and vaccine as we can see is not a diagnostic test.

Dr. Timothy Stenzel: Oh, it's very clearly a diagnostic test. It's just that it, it was moves into CBER's sphere as well and we have an agreement with CBER that we will combine our efforts to review applications that have to do with, particularly that have to do with any claims about immunity or protection. That's the situation we're really talking about here. Although they are types of assays that don't speak to immunity, all other serology assays for COVID that don't speak to immunity or protection would be reviewed within our office and our center.

Codimonte Varte: Thank you.

Coordinator: Our next question is from Lonnie Edelman. Your line is open.

Lonnie Edelman: Hi. Thanks. Good morning. I actually haven't called in a few weeks. It's good to hear all the questions and thanks for continuing the discussion. There was no template for a reader to get an EUA, so we submitted a pre-EUA a couple of months ago, maybe three months ago. I was wondering how the flow is going. You had a surge going at the beginning of the year. Are you, I guess what I want to know, if are you going to get to the pre-EUA anytime soon? Or are you still really backed up?

Dr. Timothy Stenzel: So, I think, you know, sorry for the delay in getting back to you and certainly I'm not sure that I'm aware or Toby's aware of your pre-EUA. So, if you could forward that to our templates email address and make sure that your

submission a few months ago is seen by Toby and I? We will look into it and we'll get back to you. One of us or one of the team members will get back to you. One thing with readers is in order to assess readers, we do recommend that it comes in with a candidate test.

Lonnie Edelman: Sure.

Dr. Timothy Stenzel: And that's how you assess it. So, I guess this is for general, but I don't know what you put in your submission but that's just for a general consumption. That the only way we can evaluate a reader is in the specific application in use with a test. We just don't know on the readers how, how portable they are, from test to test, right?

And we clearly have seen some issues with some readers and we're not quite sure why. It could be your individual software applications aren't robust enough but we, for example, we've seen variable performance across different makes and models. That gives us pause and, you know, something isn't robust enough to work across several makes and models, it may not be as useful. Because, you know, there's a lot of makes and models of Smartphones out there if you have a Smartphone application. And we do want to see a validation plan that incorporates diversity of Smartphone and even software version use on those Smartphones for obvious reasons.

Lonnie Edelman: Yes. That's, I have, I'm in full agreement. The system was designed with a captive phone so anyway, I don't want to turn this into an infomercial. So, we will, we'll send in the email and hopefully. Yes. Yes. I will.

Dr. Timothy Stenzel: And Toby and I will make sure you get a response.

Lonnie Edelman: Great. Thanks again for continuing to do these meetings. You know it kind of feels like things are straightening up and, you know, maybe there's no need. But there's a still at least for us.

Dr. Timothy Stenzel: For developers, I completely agree, and I have recommended to FDA leadership that for non-COVID, after we're done with COVID, that we have some kind of forum like this for all IVD and developing. It probably won't be, probably won't be a weekly call, probably will be a monthly call. But you know.

Lonnie Edelman: Great.

Dr. Timothy Stenzel: My desire and the FDA's desire is to give a ready access to developers to ask questions and to make that as easy as possible. So, it's part of our overall customer service.

Lonnie Edelman: Yes. That's great. Yes. Good to hear. Thanks so much.

Dr. Timothy Stenzel: You're welcome.

Coordinator: Our next question is from Ashwood. Your line is open.

Ashwood: Thank you. I'd just like to build on the statement that you made last week on antibody testing and on the fact that all currently approved ones should not be used for verifying immunity from vaccines. Do you foresee a series of new tests or other ones in the pipeline that would be vaccine-specific, i.e., they would be detecting specific antibodies to the Pfizer, Moderna or Johnson vaccine? And would they need to be labeled to be matched with their vaccines?

Dr. Timothy Stenzel: Yes. It's, I don't have a crystal ball that tells me how this is all going to work out. It's my hope that measuring antibody response to vaccines and post-infection, natural infection will afford some ability to speak to immunity and protection based on clinical study data. Clinical studies are being performed. They're obviously easier to perform relative to specific vaccines because you know the prior history because of, you know, studies because you've done, the investigators have done serology testing to know prior to vaccination that they haven't been exposed and are currently positive say a molecular test when they get vaccinated.

And then you know exactly when they get vaccinated, so you know the start of the immune process to raise antibody and the level of antibodies, whether or not there's neutralizing antibodies present.

So, those studies, you know, in determining outcomes from that vaccination or any sort of, obviously, infection are easiest to carryout in the vaccinated population for obvious reasons. And I hope that we don't link it to a specific vaccine but that we link it to something that is, can be universalized. This is my hope, there's no promises, but say a certain level of binding antibody to, you know, to the appropriate antigen with use of the appropriate antigen and a serology test that cross reacts with vaccine. And almost all the vaccines, well, all the ones authorized in the US are protein vaccines right now. You know I hope that there's standardization through the International WHO standard so that we can say, you know, this cut point or this level of antibody and above is protective. And we can roll that out as for use by developers in updating appropriate tests without them having to do their own outcome study with their own test.

So, the only way I can think about doing it now and I'm open to other ways is to actually utilize the WHO standard to link the study assays using these

clinical trials to the International standard. And then from there, go back through the International standard for any other developed tests. I think it would be ideal if we had a bank of immune plasma serum that could also be used to perhaps send out and blindly test developers as part of the process. Perhaps as part of the post-marked authorization process to ensure, ensure that the information that's being assessed is accurate and useful and can be counted on. So, it's a long-winded answer, a complex area right now, but one of obviously intense thought within the FDA.

Ashwood: All right. Thank you.

Coordinator: And at this time, I'm showing no further questions.

Dr. Timothy Stenzel: And we're at the end of the hour so it's good time to turn it back over to Irene.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions during today's Town Hall. Today's presentation and transcript will be made available on the CDRH Webpage at www.fda.gov/training/cdrhlearn by Wednesday, June 2. If you have additional questions about today's presentation, please email cdrh-eua-templates@fda.hhs.gov.

As you we continue to hold these virtual Town Halls, we would like to, we would appreciate your feedback. Following the conclusion of today's virtual Town Hall, please complete a short 13-question survey about you FDA CDHR virtual Town Hall experience. The survey can be found now on www.fda.gov/cdrhwebinar. Again, thank you for participating and this concludes today's virtual Town Hall.

Coordinator: Thank you for participating in today's conference. All lines may disconnect at this time.

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