FDA Virtual Town Hall Series – Immediately in Effect Guidance on Coronavirus (COVID-19) Diagnostic Tests Moderator: Irene Aihie September 23, 2020 12:15 pm ET

Coordinator: Welcome and thank you for standing by. At this time all participants are in a listen only mode until the question and answer session of today's conference. At that time, you may press star 1 on your phone to ask a question.

I would like to inform all parties that today's conference is being recorded. If you have any objections, you may disconnect at this time.

I would now like to turn the conference over to Irene Aihie. Thank you, you may begin.

Irene Aihie: Thank you. Hello, I'm Irene Aihie of CDRHs Office of Communication and Education. Welcome to the FDA 27th in a series of virtual town hall meetings to help answer technical questions about the development and validation of tests for SARS-CoV-2, during the public health emergency.

Today, Timothy Stenzel, Director of the Office of In Vitro Diagnostics and Radiological Health in the Office of Product Evaluation and Quality. And

Toby Lowe, Associate Director of the Office of In Vitro Diagnostics and Radiological Health, both from CDRH, will provide a brief update.

Following opening remarks, we will open the line for your questions related to today's discussion. Please remember that we are not able to respond to questions about specific submissions that might be under review.

Now I'll give you Timothy.

Timothy Stenzel: Thank you, Irene and welcome everyone to this week's call. We look forward to answering questions. And I just have a few brief introductory remarks. Mostly this is just going over some reminders.

So, first of all, you know our templates contain important recommendations for validation and I encourage you to check those out. And then if folks, developers submit a pre-EUA and they ask questions that can be directly addressed by the templates, in order to assist us to most efficiently handle all of the applications that we get, we are going to typically close those by referencing the relevant templates. So we hope that works. If you have questions, you know that the templates don't go into them, that's where we'll focus most of our pre EUA response. And also, if there is something that you're asking that we haven't yet created a template or posted template, then obviously, that's important for us to see and provide feedback on.

And again, the recommendations in the templates are exactly that, they are recommendations. We're are open to alternative validation strategies, we encourage you to check with us on those alternative strategies. So that we're all aligned prior to doing the work.

And then finally, I just wanted to go over some of the top priorities for review and for application processing. This is not an all-inclusive list. But does include some of them. There remains a robust interest in pooling and in particular kit manufacturers who have pooling submissions that would allow those kit users in the labs that use that kit to immediately pool with minimal work and perhaps no bench work for their own lab. That obviously greatly amplifies our efforts around trying to promote the opportunities for pooling. So those would be priority.

And then point of care tests, especially those that are molecular in antigen remain high priorities. As to those that help us to expand testing further and that includes home collection, and home testing, especially for molecular diagnostics and antigen testing.

So, with that can then move into the question and answer phase and look forward to that.

I don't believe Toby has any updates. So, she's here to assist me today. So, operator, we can go into the Q&A session.

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

If you need to withdraw your question, press star 2. Again, to ask a question, please press star 1.

Our first question comes from (Shannon Clark) from User Wide.

(Shannon Clark): Good morning. This is (Shannon Clark) from User Wide the Human Factors Consultancy. Question about PCR assay submitted for high complexity, moderate complexity and waived status. We're wondering if we could secure

the capability for pooling for just high and medium complexity contexts, but not for point of care? Does the FDA have any hesitation for approving pooling for a product just for the CLIA context, but not the point of care for that particular product? Or do you want us to do blanket testing that demonstrates that pooling is acceptable in all three contexts?

Timothy Stenzel: So that's a great question, we can carve that out and specify in the instructions that's for some high end moderately complex lab situations, there are those that have expressed interest in pooling for point of care. It would, in addition to the typical analytical and clinical validation for pooling addition, we would also want to look at usability in the point of care setting. You're not asking that for now, I'm just providing a little bit of additional information for those potentially, on the call who are interested. But we, you know, we're open to pooling schemes at point of care. But again, we would want to see that those untrained, you know, those health care workers in a point of care setting, who are not trained laboratorians can accurately carry out the pooling scheme and both convolute and deconvolute those and to get accurate results as well. I hope that's helpful.

(Shannon Clark): To be clear, if we did want to pursue point of care pooling, you're saying that human factors data would be required to demonstrate they're able to follow the pooling scheme.

Timothy Stenzel: Yes, in an actual clinical study validation to show they get accurate results doing pooling, that they don’t get false negatives and false positives and they don't mix up results.

(Shannon Clark): And are you requesting two separate city, the human factor study and a clinical study or just a clinical study that also examines user interaction?

Timothy Stenzel: I think they can be combined.

(Shannon Clark): Okay, thank you.

Timothy Stenzel: Thank you.

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

(Alyssa Crustacea): Hi, this is (Alyssa) also, from User Wide. I have a question about what has been the minimum average review time for authorization of a diagnostic PCR assay?

Timothy Stenzel: That does vary considerably because of the notification pathway for these tests. We focus our attention on the highest priority items. Everyone within two weeks of an EUA submission should have a contact that they can communicate with. And those that are the highest priority and there's room on a reviewer's desk, can be moved into that slot.

Once we move into interactive review with the reviewer. If there are no outstanding issues, the data is all there and the data looks good, And there's no additional testing that may be requested, Those applications move relatively quickly.

However, if they're priority and they get into viewers desk, but there is a substantial amount of work yet to be done and additional testing and things like that it can slow things down. So, we do encourage developers to, as

closely as possible, follow our recommendations and to pre check with us, you know, prior to doing any alternatives so that we don't lose time on either the developer side or on the reviewer's side. And also, you know if there are

problems with the review, rather with the application, where there's clearly not a match between what our recommendations are and expectations are for performance and your actual test, That's going to slow things down as well. We do look at the ponderous of evidence, but by and large, we've set our recommendations, at what we believe are very appropriate levels. So, we are asking all developers to work with us and that will speed things up for all of us.

(Alyssa Crustacea): Great, thank you so much. And thank you for doing these town halls. They're really helpful.

Timothy Stenzel: You're welcome.

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

(Ariana Trovati): Hi, everybody. So, along the same lines, I was wondering if we do end up needing to perform any new studies that were not necessarily indicated in the pre-EUA, do we lose our place in the queue by updating our submission? Or is it is the review done on a rolling basis?

Timothy Stenzel: So yes, that, you know, is mostly left up to the individual reviewer at this time. So, they don't waste time of theirs, they may hand that off to one of our other support staff, with the recommended additional study design. And then when that comes back in with that data, then that reviewer will be notified that the requested additional data has been provided. And then the reviewer as soon as they can, can get back to that.

But in order to manage all the volume of applications as efficiently as possible, those reviewers will move on to new applications. So anyways, I wanted to provide that clarity to you.

(Ariana Trovati): Thank you very much. And then for the antigen testing, about how long is the turn around right now, getting it through the review.

Timothy Stenzel: So, again, it depends, it depends greatly on the application. When we receive an application that has everything there and it's well organized, easy to understand, the data are acceptable and no additional studies are needed. Those move incredibly fast. Obviously, we're having a lot more applications right now. Versus in the early days, when we can turn things around in as little as a day. Those times are not necessarily with us right now, because of the volume. And our desire to work with as many developers as our reviewers can handle in moving them along, all along as quickly as possible. So, it does vary greatly.

So again, if additional studies are requested, that can slow things down, if things aren't clear. If study designs are not clear, we do look at more than the data, we look at the study designs to make sure that the studies were performed per our recommendations. And in that there are no potential factors that could influence our review. So, in addition to setting the data, it is great to have the study designs there.

So, the fewer questions that we that we identify in the review, the fewer questions you the developers get to answer and the faster things go.

So again, even for direct antigen, when those submissions are well put together, well organized, everything looks, you know, shipshape, then those can go incredibly fast.

(Ariana Trovati): Thank you very much.

Coordinator: Our next question comes from (Daniel Marcus), your line is now open.

Timothy Stenzel: Hey, Dan how is it going?

(Daniel Marcus): So, my question and I've asked a shade of this before is around EUAs for point of care tests. To my knowledge, to date most of them have just been platforms that you're familiar with that have basically developed an assay for those platforms. I know we mentioned or last time I asked question to the nature, I mentioned the notion of there being an assay that requires a pipetting step. And that being something that you guys would probably consider to be a fairly complex thing. Whereas I've seen other assay that have gotten point of care designation that use something that will not, rather not precision pipetting, but a transfer pipetting step.

And so that's the specific question, which is, could the substitution of a simpler liquid transfer mechanism taken assay from being a highly complex assay to a CLIA waived point of care assay? And then the broader question is, what are the fundamental components of an assay that you would deem to be something that you would authorize for the point of care that isn't an existing platform? Because I think there's a lot of developers are trying to crack that code. And I know, to date, I don't think I've seen one that that's been able to successfully do it. So, I'm just wondering what that looks like.

Timothy Stenzel: Yes, I'm trying to find the list. We had a list of point of care tests that we've authorized recently, and there are quite a few that that we've authorized that have not previously been seen by the FDA. And I know that I think the molecular template we're updating with point of care studies, but the antigen,

template and I believe the serology template have point of care studies, or vice versa, maybe I forget, Toby can probably clarify which, which template has the point of care.

Toby Lowe: You're correct.

Timothy Stenzel: So, you can you can look at it, first of all, we can provide those recommendations for, for technology point of care that we haven't had posted now. It won't be, you know, it won't even be a draft template and just be specific recommendations relative to the question, but we absolutely have authorized new point of care devices. I'm trying to find that list. Maybe Toby, you have that list? I know it was shared recently on an email.

Toby Lowe: Yes. And actually, we were both backwards on the template. So molecular template does have point of care, antigen does not but will be updated with it. For point of care tests, there are I believe, nine currently authorized. Five molecular and four antigen. And I think I want to say that there's about three molecular and two antigen, possibly, that are platforms that we have not previously seen before the pandemic.

(Daniel Marcus): And what would you say are the commonalities between those as far as how you look at complexity, or is it very, very much a case by case thing?

Timothy Stenzel: No, there's pretty good, you know, if you wouldn't mind indulging us, Toby, you could read through those one by one, and I'll tell you whether it's new. I'm having a hard time finding this list quite easily.

Toby Lowe: The antigen tests that have been authorized for point of care are the Abbott BinaxNow.

Timothy Stenzel: So, for Abbott we've previously seen that device and authorized it for other targets such as the flu, I think. So, we don't ask them to do -- if the workflows, basically exactly the same, we don't ask them to do the guard band studies for this. I'm forgetting the exact terminology we use. But the study is around, you know, what are the volume parameters that are important to watch and the time parameters. So, workflows the same, we don't ask them to repeat that, that's just a way to speed things to market, but it's a new device. And there's a pipetting step. First of all, precision pipetting with the calibrated pipette is not something that most CLIA waived labs have and nor are those healthcare workers trained in it's correct operation. However, most of the point of care devices, if they have a pipetting step, they have a little bulb, plastic bulb pipettor is common. You know, and so that's what we look for, things requiring centrifugation, things requiring vortexing, things requiring freezers, those are all you know, a little bit different.

We will take them all one by one and assess them as to whether or not a CLIA waived environment worker can properly operate them. We are taking for at least this pandemic and in order to speed things along, we are maintaining a very open mind. That may, you know, as far as this, it may. And I think we are being very flexible and allowing some things that outside of this pandemic situation, we might not.

Again, the designation of waived status here is not - it's deemed, not actually formally classified. Formal classification for CLIA waiver would happen upon conversion to a full application at some subsequent point if that's what the developer does.

So, these are in essence, temporary, deemed waived status, so Toby, if you continue on.

Toby Lowe: Yes, so the next one is LumiraDX test, which is the only one of the antigen tests, I believe, where we had not seen the instrument before the pandemic.

Timothy Stenzel: Yes. So, you know, obviously, they then have done the point of care studies that we've recommended for that setting that was a direct antigen test. And so, you can look to that IFU to know the studies that they performed.

Okay, next one, and just moving to well, the other antigens are probably Quidel and BD Veritor, obviously, we've already authorized waived tests for them. So again, we deemed without requiring them to do the repeat point of care studies for this pandemic.

Moving to molecular then, Toby.

Toby Lowe: Yes. So, we have the Cepheid Xpert Xpress.

Timothy Stenzel: So that's obviously something that we've waived before very commonly used instruments, next.

Toby Lowe: Abbott ID now.

Timothy Stenzel: Again, very commonly used and waived before, next.

Toby Lowe: Roche Cobas for the Cobas Liat.

Timothy Stenzel: Liat. Yes. So again, we've authorized that for flu and other targets before, next.

Toby Lowe: The Mesa Biotech Accula.

Timothy Stenzel: I believe we've already authorized the mesa one for flu. So that was not new to us. Next.

Toby Lowe: The Cue Health. I believe that was new.

((Crosstalk)

Timothy Stenzel: That was new, and they performed all of the point of care studies. And you can look their IFU to see some of the same, and not all the studies that were performed for that, next.

Toby Lowe: I believe that's all of them.

Timothy Stenzel: Okay, so there were two that were new.

(Daniel Marcus): By my count that's two. I guess it illustrates my point a little bit.

Timothy Stenzel: What's your point?

(Daniel Marcus): My point is that it's to try to find the commonalities with respect to what's considered not complex enough for the least complex to be able to authorize

for point of care setting is somewhat, is somewhat opaque. And I guess what I'm trying to find, is figured out if there's enough, what are the ingredients that make something point of care outside of us having all waived them before.

Timothy Stenzel: The bottom line than an untrained user that is a healthcare worker in a CLIA Waived of setting, a clinic sort of setting. And now in this pandemic, it could be a school setting with a waiver, a certificate of waiver, or a work certificate of waiver and not anybody related at all to a health care facility in the prior, that they can open up the box, read the instructions perform the test accurately and get acceptable results. Bottom line, that's what it is. And they don't have, they don't have a laboratory setup. So, the more everything is self-contained within the kit, the better. The fewer the steps and reading the results and interpretation of the results should be straightforward.

Typically, in that kind of CLIA waived of setting, you don't even have a long instructions for use. You have a quick user reference instructions, mostly pictures. Think of you know self-assembly of some, you know, home you know, furniture you might get from a store, from IKEA.

(Daniel Marcus): IKEA may not be your best analogy for your point, but I do get it.

Toby Lowe: And we do have quite a bit of information on our website about how we assess tests for complexity outside of pandemic. And while it's not, you know, completely the same situation because as Tim explained, these are not formally categorized during the EUA review they're just deemed waived for the purposes of the pandemic, we do consider the, you know, the information that we consider during a formal complexity review, we just may have a slightly different bar, you know, given the risk benefit analysis for the pandemic. But there is a lot of information about how we assess the

simplicity of a test to determine whether it's appropriate for a CLIA waived setting.

(Daniel Marcus): You devoted a lot of time to this, and I appreciate that. So, I'll seed back. But thank you. I appreciate it.

Timothy Stenzel: Operator.

Operator. Our next one comes from (Lin Hong).

(Lin Hong): Hi, Dr. Stenzel. Thanks for taking my call. My question is about priorities and how you see that potentially evolving over time. Particularly, I think right now, it does make sense that, you know, serology is taking a bit of a backseat to active virology testing, whether it's PCR or antigen. I was wondering if you could comment in a post-vaccine world where folks are getting vaccinated, you know, what is the value of testing for serology? And in terms of characterizing individual immune response and potentially monitoring antibody response over time. Certainly, I recognize some of this data continues to evolve. But when you do the math in a post- vaccine world, you could see the demand, you know, getting up to millions, if not hundreds of millions of tests required.

So anyway, I just was wondering what are your thoughts on that?

Timothy Stenzel: Yes, it's a great question and a little bit more transparency, and not that I didn't want to offer it before. But we have three teams, three separate teams, those who are expert at molecular, those who are expert at antigen and those that are expert at serology. And they are independent of one another and have their own priority of it. So, this serology team, you know, is 100% on serology. They're not they're not working on antigen; they're not working on molecular.

They are 100% serology. And we do have the ability to shift resources from one team to another to balance the workload. And we have been actively rebalancing, when appropriate. But by and large, there's a core group in each of those areas who have a long history of working with developers for their specific technology, who are dedicated to those. So, serology for the serology team is all they're focused on and they're moving as quickly as they can.

And then I think I may have missed the second part of the question.

(Lin Hong): Yes, I was just wondering, you know, in the post vaccine world, you know, that potentially, you know, measuring antibody response, monitoring that because I think the data is still coming out and may vary by vaccine may vary by ethnicity? How long do people retain those responses? Because I could see, or I guess, one could see that, you know, the demand could be quite considerable, depending on how the clinical data evolves.

Timothy Stenzel: I think you're absolutely correct. And it's why, you know, we have a team dedicated to serology and advancing serology and will remain dedicated to that. When you move into a vaccine situation and you then start to potentially ask questions or try to answer questions relative to vaccines that does become a little bit more complex from a data perspective. And you know, if you want to have some sort of claims around, you know, showing response say to a vaccine and whether that response is adequate or not, et cetera, et cetera. The agencies, you know, we'll take a look at those requests. I can't foretell exactly what our response would be. And it frankly, it would not involve just our Center and our, you know, our OIR Office, but likely other areas of the FDA, as you might expect, so. But again, you know, we remain open to ideas and open for business. So, if you want to start having those dialogues with us now, we're open to it.

(Lin Hong): So absolutely, thank you for taking the time and your thoughtful comments. Thank you.

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

(Peggy McLaughlin): Thank you, Dr. Stenzel. For taking questions this morning. In the development of an antigen test for home use, we'd like to use a PCR assay whose intended use is specific for a nasal pharyngeal swab, but due to expected patient comfort and compliance, we'd like to use a mid-turbinate swab. Is this allowable with discussion with the FDA per your guidance? And what kind of discussion would that be? Or does the FDA require use of only a PCR test? Who has been - which has been authorized for mid terminate sampling?

Timothy Stenzel: So, I think you're saying, "Can you use a molecular test off label that's been authorized for a validation purposes?" And I think you're looking at developing and validating an antigen test in the home. Can I ask you this? It's a swab based test you're developing.

(Peggy McLaughlin): Yes.

Timothy Stenzel: And you want to use a mid-turbinate?

(Peggy McLaughlin): Potentially.

Timothy Stenzel: Okay. Well, we are very open to a home mid -turbinate use. And I don't know that we've authorized a mid-turbinate, but we've certainly expressed that in multiple occasions. The only caveat to that is in the home environment, we want to look at whether children would be swapped or not with a mid-turbinate. And if so, there are stoppers or other devices that can be utilized

with a mid-turbinate swab that makes it appropriate for kids and it can be removed for adults. So that's the only sort of caveat on mid-turbinate. It would be unlikely for a direct antigen test to be more sensitive

than a molecular test in the home situation. So, we want to compare it to an authorized version of the test, an EUA test, and typically I think in our recommendations, we say a high sensitivity test. And that can be performed in a lot of different settings. We're open to entirely in the true truly home setting. But you can also do have the users come into a simulated home environment and do testing. And then obviously, after they've collected the sample for your home test and tested it, they can be swapped by a healthcare worker and then sent in for an EUA authorized test.

So probably some of those details that you're talking about, you know, would best be worked out with one of our review staff. So, if something is again, an alternate sort of pathway, then in our recommendations for the template from the home test template, then I would reach out through our templates email address and asked those specific targeted questions.

(Peggy McLaughlin): Hey, thank you, Dr. Stenzel.

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

(Elliot Cowan): Alright, thanks. This is a question about standard development for quantitative anybody assays. So usually, I'm sorry, WHO generates internationally recognized standards for infectious disease tests. But it looks as though CDC is making its own standards for the antibodies recognizing different SARS-CoV-2 proteins. Will FDA have a preference between the CDC standard and the WHO standards? Since FDA is usually a key player in

WHO standard development? Or will the standards from WHO and CDC be aligned?

Timothy Stenzel: You know, that's a question I don't know the answer to right off the top of my head. We are open to any - to considering any international standard. We're obviously working with the WHO. Toby, are you aware specifically is the CDC doing something separate? Because I know that in all likelihood there are multiple parties within us government involved in the WHO standard development, not just for serology, but for antigen and molecular tests as well.

Toby Lowe: No, I'm not aware, that's probably a question better for the for CDC. And I think generally we would, you know, be involved as much as possible and evaluate whatever standards are, are put out prior to commenting on them.

(Elliot Cowan): Yes, because Siemens recently released a press release and they talked about how they were involved with CDC and development of serology test standards.

Timothy Stenzel: Yes, I would, you know, will in will independently reach out to the CDC, but I would recommend that you directly approach the CDC and try to and try to get some clarity from them. Okay.

(Elliot Cowan): Okay, yes. Thanks.

Timothy Stenzel: You're welcome.

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

(Ian McLeod), your line is now open.

(Ian McLeod): Hi, this is (Ian) from Adaptive Bio Scientific. Can you hear me?

Timothy Stenzel: Yes, we can.

(Ian McLeod): Okay, great. So, we submitted our EUA on the 15th of May for panda technology, which is a QPCR method which is unaffected by mismatches in the primer binding site. And these are known to impact conventional QPCRs looks like what we're seeing with the Roche assays, which is starting to fail due to the IG mutations. Now, since the 15th of May, we submitted three amendments, including one for saliva as a sample type. And our customers have performed over 65,000 tests using our kits. And we've had no adverse events or complaints.

Now, we were initially assigned a reviewer and then told on the fifth of June that the assignment had been an error and that no reviewer has been assigned. Then since then, we've received no meaningful updates in the last almost four months. So, who should we be contacting to request the reviewer be assigned?

Timothy Stenzel: So hopefully, you have some sort of contact in our office so that you can ask questions and we get updates on a weekly basis, that is my direction. But in this particular case, because it's been so long, I would like to understand a little bit more detail. So, if you send an email to our cdrh-eua-templates@fda.hhs.gov email, the common email address for this pandemic for covid related tests and ask for Doctor Stenzel or Toby Lowe and we will look into details and either communicate directly with you or have someone else get back to you.

(Ian McLeod): Great, thank you very much for very much appreciate it.

Coordinator: Our next question comes from Oregon State Public Health Lab. Your line is now open.

Man 1: Hi, Dr. Stenzel. Thank you for taking this question. We're developing or validating a lamp assay using the CDC PCRS is a reference test and I'm wondering, what is the benchmark for sensitivity and specificity for this test? It's going to be used as a point of care test. And we're going to try to send. You're saying no.

Woman 1: No. It's going to be used as a high complexity test. And we're going to put it in the certified high complexity laboratory.

Man 1: Thank you that was Sherry.

Timothy Stenzel: Hi, yes, no, that's fine. You know, we've really recommend that no that no viral detection test, single use, you know, whether it's antigen or molecular fall below an 80% percent positive agreement of PPA or in other you know kind of another term for sensitivity. You know, we ideally would like to see, you know, a sensitivity of greater than 95% greater than or equal to 95% in comparison to an EUA authorized by sensitivity molecular test. But we can authorize, if it falls below that 95. There may be some limitations in the language such as negatives may be presumed negative, rather than negatives. So, we are open to new technology that fall below that standard molecular comparison target, even in the high complexity labs.

Woman 1: Do you, this is (Sherry), a follow up question. Do you have a marker for the limited detection, like 100 virus copies or 1000 virus copies, like I know, when I looked at your website, it seems like the limits of detection are variable.

Timothy Stenzel: So, you know, each developer performs limited detection studies so that, in in their authorized test, users can see not only how they did it, but what the termination is. And, and those methods can vary greatly and have been very

varied throughout this pandemic. Early on when samples or all virus was not even available. Now, we do recommend that live or inactivated virus be used for those LOD studies. And then, we also now have the FDA reference panel. So, developers who have a locked down device and would like to initiate the testing of their device using our relative LOD FDA reference panel can request that panel and on a case by case basis for those who haven't yet submitted even in EUA, we will look at that those who have submitted an EUA can request that now as well. And obviously, those who have an EUA authorization, we have been contacting all EUA authorized test developers asking for shipping information and then sending them the panel and working with them. And working on determining with that panel, what we can say about the relative LOD using the FDA panel and then obviously working to post those results which we already have.

So long winded answers saying a lot of different things taking pause there if you want any clarification.

Man 1: I think we're fine. Thank you very much.

Timothy Stenzel: You're welcome.

Operators: Our next question comes from (Daniel Roth). Your line is now open.

(Daniel Roth): Yes, hi, Doctor Stenzel. Thank you. So, a question here are related to positive predictive value for home use diagnostic kit and positive traits value for home use surveillance kit. They come in multipack format. Curious how

you view the differences between those two uses as well as what is an appropriate number of subjects for a usability study for an at home test?

Timothy Stenzel: Is this for serology? Or is this for direct antigen or molecular?

(Daniel Roth): Sure, this is for an antigen test.

Timothy Stenzel: Okay, for antigens. So, and I understood home use diagnosis and then I'm not sure if you meant screening when you saying surveillance or are you talking truly surveillance as we have defined on our FDA FAQ webpage. Surveillance being that you're not really providing a CLIA result. You're doing population assessment of the presence or absence and at what level of the virus in it, in a targeted population basis.

(Daniel Roth): Yes, it would be a bit, good thing, to understand the differences, and the positive predictive value recommendation for screening, versus diagnostic, for at-home use and if the word surveillance means something in this context as a third category, then it would be good for us to know the numbers you recommend for a single test, as well as what's an overall multi pack? Assuming it's a two or three multi pack, what the overall positive predictive value should be.

Timothy Stenzel: All right, so, yes. So, for truly surveillance purposes as defined in our FAQ, and you can go there, for this pandemic, the FDA is not reviewing those. We do obviously recommend that in those situations an EUA authorized test be used, but it's not a requirement. And there are different, you can check with CMS and in CLIA, there are different reporting, you know, there I don't believe there's reporting requirements, but double check with them.

So, for home use diagnosis, that's somebody with symptoms, home use screening, for those who may otherwise be at risk and could be asymptomatic carriers. There are clear recommendations in our templates, if you go to our template at the FDA website for what's probably called home use testing includes both molecular and antigen recommendations for that environment, it has all the recommended performance expectation.

When you're talking about PPV, there's difference between PPV and PPA positive predictive value versus percent positive agreement. Percent positive agreement is when you're comparing your method to some other method. We recommend EUA authorized high sensitivity molecular test. That's really looking at you know, when the reference test is positive, how many times out of 100 is your test that you're developing positive? So, if it's positive, say, you know 90% of the time when the high sensitivity molecular test is positive, then your PPA or sensitivity would be 90%. Positive predictive value has to do with it's more of a population based measure. Yes, we do look at PPV for direct antigen tests, but that PPV can vary widely depending on the percent positivity in a given population. When a population has a very low incidence of active coronavirus infection, you know, a test like indirect antigen test that may have a specificity of 99%, would have quite a low PPV. I think I mentioned recently, that if the prevalence of SARS infection detectable with a direct antigen test is 0.2%. The test is 99% specific, the positive predictive value is 16%. So, you know, basically five out of six positive results are false positives. And that doesn't mean there's anything wrong with the test. It just means that in a low percent positive population, you're going to, even with a relatively high specific test, like 99% pretty high. Hard to go above that significantly within with a direct antigen test. You just want to confirm those results, I think with another test.

So, we don't have typically a specific recommendation for PPV. We do have expectations for specificity and sensitivity or PPA and NPA. Negative percentage agreement and positive percent agreement. And we would for direct antigen test as for molecular tests in the home environment, when it's done by prescription, it's the same expectation as any other and viral detection method and that is what I like to see.

For single use, we'd like to see 80% PPA or sensitivity or greater. We are open, as we've stated, as (Jeff) and I stated in our recent op ed in the hill, we are open to a lower single test PPA. You know, we mentioned 70%. If some sort of serial testing, a two- pack, perhaps have the test done on consecutive days or in days 1 days 3, is able to in a combined sense, get us to that 80% mark, we may indeed find that acceptable.

And again, as I've stated on previous calls, at this forum, we're most interested in identifying patients in the first 5 to 7 days of infection, when they have the highest viral load. That is viral loads that we think might very likely, although it's hard to get at this, corresponds to their ability to infect others. And so, we want to make sure we identify those people and we have a test that's sensitive to detecting those.

So far as far as you have any clarifying questions?

(Daniel Roth): Sure, that's extremely helpful. And the other question was about an appropriate number of subjects for a usability study that we may recommend?

Timothy Stenzel: Yes, it that is that is in the home, I believe that's in the home test template that's on our website. And I don't remember I want to be accurate. Toby, unless you know, specifically, what that number is. I would just refer you to that. And then if you have any follow up questions, if the templates not clear,

just send us an email to the templates, email address. Toby do you know. If not, that's fine.

Toby Lowe: No, I don't have I don't have the template open.

Timothy Stenzel: Yes, I think Yes, rather than taking time to pull that template up and find that section we have. There's a lot of information in those templates. And I would appreciate that.

Thanks for your questions.

Coordinator: Our last question comes from (Han Son). Your line is now open.

(Han), your line is now open.

(Han Son): Hello. Can you guys hear me?

Timothy Stenzel: Yes. can hear you now. Thanks.

(Han Son): Yes. My question is pertaining to point of care testing. With regards to the six further components of robustness testing. And one of the elements requires the test to be performed at high temperature. I was just wondering about how you rationalize the need for doing the test at 40 degrees Celsius when the average temperature around here is not even that extreme conditions? And is it really required for us to do that type of a temperature stress test, for point of care testing?

Timothy Stenzel: So those are our recommendations. If you want to propose alternate, that's fine. We may put limitation, temperature limitations, in your instructions for use. But we are seeing that these kind of point of care tests sometimes are used and in non-healthcare settings now, that may not have air conditioning.

And so, in sometimes they're pop up tents and things like that. So that's the reason for asking that kind of temperature variation.

But again, you know, we can label around certain potential, we have the option, when everything else looks good to look at whether or not we alter the labeling for your product. And it might say if your test, for example, doesn't perform well, we might say must be performed in, in temperature controlled environment between these temperatures. But it's really working with you to figure out when your test performs well. So, you know, so we asked for these flex studies. And we want to see if there is any impact on your test performance. And then It doesn't necessarily mean if there's an impact that we wouldn't authorize your test. It's simply that we want to alert users, that certain variables may impact the performance of the test. So, I'll pause there in case you have any clarifying questions.

Hopefully that was clear and justifies why we asked those important questions.

(Han Son): Okay, thank you. Thank you very much.

Irene Aihie: Thank you. I believe that was our last question. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcripts will be made available on the CDRH learn webpage at www.fda.gov/training/cdrhlearn by Thursday, October 1.

If you have additional questions about today's presentation, please email cdrh-eua- templates@fda.hhs.gov. As always, we appreciate your feedback.

Following the conclusion of today's presentation, please complete a short 13 question survey about our FDA CDRH virtual Town Hall experience. The

survey can be found at www.fda.gov/cdrhwebinar immediately following the conclusion of today's live discussion. Again, thank you for participating in this concludes today's discussion.

Coordinator: That concludes today's conference. Thank you for participating You may disconnect at this time. Speakers, please allow a moment of silence and standby for your post conference.

END