CDRH Virtual Town Hall #99
Monkeypox (mpox) and COVID-19 Test Development and Validation
December 14, 2022

CDR Kim Piermatteo: Hello, and welcome everyone to today's Virtual Town Hall number 99 for monkeypox or mpox, and SARS-COV-2 test developers. Today we will discuss and answer your questions about diagnostic tests in response to the mpox and COVID-19 public health emergencies.

This is Commander Kim Piermatteo of the United States Public Health Service, and I am the Education Program Administrator within the Division of Industry and Consumer Education in CDRH's Office of Communication and Education. I'll be your moderator for today's Virtual Town Hall.

Our panelists for today are Dr. Timothy Stenzel, Director of the Office of In Vitro Diagnostics, which is also referred to as the Office of Health Technology, number seven, or OHT7, in CDRH's Office of Product Evaluation and Quality or OPEQ. Joining Tim is Toby Lowe, Associate Director for Regulatory Programs in OHT7, and Dr. Kristian Roth, Deputy Director of the Division of Microbiology Devices in OHT7, and Dr. Noel Gerald, Branch Chief for Bacterial Respiratory and Medical Countermeasures in OHT7 as well.

For today's Virtual Town Hall we'll begin with opening remarks, and then we'll answer your previously emailed questions. And then lastly we will address your live questions. As a friendly reminder for those of you participating live in today's virtual town hall, please be sure you have joined us via the Zoom app and not through a web browser to avoid any technical issues.

Our next Virtual Town Hall will be held on Wednesday, January 11, 2023, for both mpox and COVID-19 test developers. You may refer to our web page titled “Medical Device Webinars and Stakeholder Calls,” specifically our “Virtual Town Hall Series - Test Development and Validation During Public Health Emergencies for COVID-19 and Monkeypox” web page for details on all upcoming virtual town halls. Links to both of these web pages have been provided on this slide.

The presentation and transcript for our last Virtual Town Hall, which was held on November 30, 2022, have been posted to CDRH Learn. I have provided a screenshot on this slide where you can find those materials within CDRH Learn.

I'd now like to welcome Toby, who will provide today's opening remarks for mpox and COVID-19. Toby, the floor is yours.

Toby Lowe: Thank you, Kim. Thanks, everyone, for joining again for another town hall. As Kim mentioned, this will be the last one of 2022. So we also wish you all a happy holiday season and end of year. So just a couple updates. As I'm sure most of you are aware, in response to the World Health Organization action, the FDA is adopting the mpox name from this point forward. We have begun to reflect this change in web content and other written material prospectively.

Additionally as we've mentioned previously, we've responded to some of the pre-EUAs for mpox tests to let sponsors know whether or not we would be prioritizing review of their test, and we have begun review of some EUA requests accordingly. If you have not yet received a response on your pre-EUA, please just note that we are still considering some of those in the context of the shifting needs of the public health emergency, and we will get back to you with a response as soon as we're able to.

Moving to COVID-19 updates, just yesterday we updated the SARS-COV-2 viral mutations web page that discusses the impact on COVID-19 tests. And that update was to add an additional entry for the Luminostics' Clip COVID Rapid Antigen Test, where the sensitivity may be impacted when a patient sample containing the virus with certain mutations is tested. Excuse me, additional information is up on that website for that test.

And with that, I will hand it back to you Kim.

CDR Kim Piermatteo: Thanks, Toby, for those remarks. Alright, we will now address or answer, sorry, your previously emailed questions about mpox and COVID-19 test development and validation. As always, please note we do receive some emailed questions that are too detailed or test case specific that we will not address during today's town hall. For those questions, we will try to send a response in writing within a few days.

If you have submitted a question and do not hear it addressed today, please look for a written response. If you do not receive a response within a few days, please feel free to reach back out to the MPXDx@fda.hhs.gov mailbox, or the COVID19Dx@fda.hhs.gov mailbox for an update. Also we have received some specific questions as a follow up to FDA feedback from pre-EUA or Pre-Submission requests, that we will not address during today's virtual town hall. For those questions we encourage you to contact your assigned lead reviewer to discuss or submit a supplemental request.

Toby, I will be directing these previously emailed questions about mpox test development to you. The first question is a series, so it's a series of questions that pertains to mutation monitoring in mpox tests.

For the first part there is one question. The mutation monitoring section of the mpox submission template states, monitoring should include identifying if there are multiple credible reports indicating that a given viral variant, which may have one or more mutations, has the potential to increase virulence, increase transmission, or otherwise increase the public health risk. The question is, can FDA clarify what credible reports are appropriate?

Toby Lowe: Thanks, Kim. So we do recommend using peer reviewed literature, or in the more immediate term, using reports from public health communities, from the public health community, such as state public health laboratories. There may also be other situations where a test developer receives a signal that there may be an issue, and that's something that would be considered on a one-off basis, since monitoring for impact of mutations is a very important aspect of maintaining test performance.

CDR Kim Piermatteo: Thanks, Toby. So for the second part of this question, there are three questions. To give context it says, the mutation monitoring section of the mpox submission template states, if the mutations are found to be critical to your test design, such mutations and variants should be evaluated using clinical or contrived, as available and as appropriate, samples to assess the impact of the mutation or variant on your test performance. The aggregate impact of the mutations should not reduce the clinical performance of the test by 5% or more or decrease the clinical performance point estimates for the test below the minimum clinical performance recommendations. The first question for this part is, what does a reduction of clinical performance by 5% or more mean?

Toby Lowe: Thanks Kim. So we consider a reduction in clinical sensitivity of 5% or more from the previously established performance, which is the performance reflected in the authorized documents

for authorized tests, or a decrease in the test performance to a level below the performance recommendations in the applicable EUA templates.

CDR Kim Piermatteo: Thanks Toby. So the second question of this part is, if clinical performance is defined by positive percent agreement or PPA, what testing clinical samples compared with a high sensitivity comparator method, how are data generated from current viral sequences, though in silico or wet testing with contrived samples correlated to the original clinical study?

Toby Lowe: So if a test is expected to fail due to a mutation, and by fail we mean return a false negative, fail to detect the virus, and that mutation that would cause that failure is in more than 5% of currently circulating virus sequences, then we consider the test to be at risk of exhibiting a performance decrease of at least 5% of the performance in the EUA labeling, where which is the performance that was generated using clinical samples without that problematic mutation.

CDR Kim Piermatteo: Thanks again, Toby. So the last and third question of this part is, are we to consider a download of current strains within a certain time frame to be indicative of all circulating strains since submission?

Toby Lowe: Thanks. So we do recommend monitoring on at least a monthly basis, as well as if requested at any point by FDA. And if FDA requests records, we expect that records of these evaluations be submitted for FDA review within 48 hours of the request.

CDR Kim Piermatteo: Thank you, Toby. Alright, we will now move to address a previously emailed question related to COVID-19 test development. And Toby, I'll be coming back to you for this one.

So Toby, the question is, in the feedback we received regarding FDA'S recommendations for submitting a 510(k) for a COVID-19 test, the FDA recommends for a device intended for point of care or POC or at home use that the reagent stability study should include a storage condition of high humidity at 30 degrees Celsius. Can the FDA clarify if high humidity is required for the duration of the real time study?

Toby Lowe: Thanks, Kim. No, the high humidity condition is not required for the duration of the real time reagent stability study. High humidity at 30 degrees Celsius can be evaluated in a flex study that can be performed across seven days. Flex studies typically are used to assess the robustness of an assay through appropriately designed studies to challenge the operational limits of the test system, by simulating conditions of use outside of the intended use environment.

That may include potential use errors, and anticipated environmental stresses, such as temperature and humidity extremes. Flex studies should be conducted to the point of failure to determine the maximum deviation that will allow for generating accurate results. And if your device is intended for distribution into high humidity climate zones, under conditions that can't easily maintain the recommended storage conditions, then it is important to ensure that your product maintains shelf life under those conditions. So that is one situation where you would want to consider a flex study like this.

CDR Kim Piermatteo: Thanks again, Toby, for your responses. So that wraps up the previously emailed questions for both monkeypox and COVID-19 test development. We will now move to address your live questions. To ask a live question, please select the Raise Hand icon at the bottom of your Zoom screen. When you are called on, please follow the prompt in Zoom and select the blue button to unmute your line. Then identify yourself, and then ask your question. Please remember to limit yourself to asking one

question only. If you have an additional question, you may raise your hand again to get back into the queue, and I will call on you as time permits.

So it looks like our first question is coming from Judy. Judy, I have unmuted your line. Please unmute yourself and ask your question.

Judy: Hi, this is Judy. Thank you very much. So my question is about the labeling, FDA authorized delivery of the EUA test kits. If we are a manufacturer and we got the authorized delivery for our produced labels, I don't know if the elements are same with the authorized labeling, but only the layout is a little bit different. The location of the elements is a little bit different. Could we still distribute those?

I mean the outside box of the test kit.

Timothy Stenzel: Yeah, if you're going to make any changes to labeling, go ahead and submit that to the reviewer that reviewed your original application, and ask the question specifically. We would want to look at what you're doing, and not handle the question over the phone here.

Judy: I see, so we need to submit for review previously, right? Even though all of the elements are the same. Only the location is a bit different.

Timothy Stenzel: So it's a very specific question that I think is best handled offline.

Judy: OK.

CDR Kim Piermatteo: Yep, thank you, Judy. Thank you, Tim. Alright, I don't see any more raised hands, so I'm going to go ahead and make a call out. If you have a question you would like to ask our panelists today, please raise your hand.

I don't see any more raised hands. Tim or Toby, did you have any other remarks you wanted to provide? Or we can move to close early today. I think people are getting ready for the holiday.

Timothy Stenzel: No, other than to say we'll be planning a town hall in January. I'm not sure if you mentioned it already, but we'll get that information out soon. OK?

CDR Kim Piermatteo: OK. Tim, Judy, has one more another question. I'm going to call on her, and we will see. Judy, I unmuted your line. Can you ask your question, please?

Judy: OK, it's really lucky today, so I have a second question. My second question is that for the 510(k) performance test kits, if they do require that, is it recommended as to use live virus?

Timothy Stenzel: So, is that for an antigen test, or a molecular test?

Judy: Antigen test.

Timothy Stenzel: And this is for COVID?

Judy: Yes, COVID, COVID.

Timothy Stenzel: Antigen test for COVID. So you can, although that is a BSL 3 level virus. So there are, if you can use inactivated virus, if you show it works fine. Kris, do you have any other recommendations?

Kristian Roth: I believe if you have a similar LoD and you can establish similarity between live and inactivated virus. Potentially we would take inactivated virus for some of the clinical studies, but again, this is a question that should come in through Pre-Sub. You'd want for us to really understand what your proposal is so there's no kind of miscommunication once you submit that data to us.

Judy: Oh, OK. Thank you. Thank you very much. So if I understand right, is that I mean live virus is not a must. To talk with our reviewer, pre-EUA reviewer, right?

Kristian Roth: Yes, that would be helpful. If you have a pre-EUA reviewer, reach out to them with that simple question, and they should be able to get back to you.

Judy: Oh, OK. Thank you very much.

CDR Kim Piermatteo: Thank you, Judy. Thank you, Tim and Kris. Alright, at this time I do not see any more questions. I will go ahead and move to close today's town hall.

So today's town hall presentation and transcript will be posted to CDRH Learn under the section titled In Vitro Diagnostics, and the subsection titled Virtual Town Hall Series. Again, if you have any additional questions about mpox test development, you may send an email to MPXDx@fda.hhs.gov. And for additional questions about COVID-19 test development you may send an email to COVID19Dx@fda.hhs.gov.

As a friendly reminder, and as Tim had mentioned, our next Virtual Town Hall will be for mpox and COVID-19 test developers on Wednesday, January 11, 2023, from 12:05 to 1:00 PM Eastern time.

This concludes today's Virtual Town Hall, and our town hall series for the calendar year 2022. Thank you all for joining us today, and over this past year. We wish you all a very happy new year.

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