CDRH Virtual Town Hall #101
mpox and COVID-19 Test Development and Validation
February 15, 2023

CDR Kim Piermatteo: Welcome everyone to today's Virtual Town Hall number 101 for 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 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 town hall, we'll begin with opening remarks, then we'll answer your previously emailed questions, and then, lastly, we'll address your live questions. As a friendly reminder, for those of you participating in today's virtual town hall live, please be sure you've joined us via the Zoom app and not through a web browser to avoid any technical issues.

For your information, the presentation and transcript for our last virtual town hall, which was held on January 11, 2023, have been posted to CDRH Learn. A screenshot has been provided on this slide of where you can find those materials within CDRH Learn. I'd now, like to turn it over to Tim for his opening remarks. Tim.

Timothy Stenzel: Yes. Thank you, Kim, and hello, everyone today on the call. Welcome. I wanted to make the announcement that this town Hall will be the penultimate regularly scheduled town hall for both monkeypox or mpox and COVID. The last planned town hall will be next month in March. While the 564 IVD EUA declarations remain in place for both, and Toby will say a little bit more later, at least about COVID.

We are winding down IVD review activities for EUA, focusing on finishing what has already been started, i.e. submitted and accepted for review and under review, as well as, a small number of remaining anticipated priority submissions that will likely come in, in the future. And we will, of course, schedule additional town halls should the need arise.

We have received much positive feedback over time that these town halls have been very helpful to the development community. We are humbled and honored to have been part of this. Rest assured that we plan to utilize this avenue of communication whenever the need should arise in the future. Going forward, questions about EUAs for mpox and COVID can still be sent to the email inboxes for both. And if you have a submission, you can reach out to your assigned contact at the FDA.

OK, we'll turn this over to Toby, then. Toby.

Toby Lowe: Thanks, Tim. So I will go through a couple updates and then we will get into the previously submitted questions. So first, for mpox, we just wanted to share that a few days ago, we authorized the Cepheid Xpert mpox test, which is the first mpox test authorized for use in a point-of-care setting. And that validation data for that EUA was gathered through the NIH ITAP program.

For COVID, we have a few updates. In January, about a month ago, we issued a level two update, so minor policy updates, to the COVID-19 test guidance, as well as the viral mutations policy guidance. Those updates were to reflect that the guidances will be in effect for the duration of the Section 564 declaration, rather than the 319 Public Health Emergency. So that basically, affects the plan going forward-- as Tim was just talking about-- with the 319 expected to end in May, and I'll get into that a little bit more in a minute.

We also updated-- some minor updates in the mutations guidance. That one hadn't been updated in a while so we updated some language to match the September 2022 update to the test policy guidance-- encouraging submissions of traditional premarket review submissions, added some links to additional web resources that we've put in place since the initial version of that guidance, and updated some of the actions we've taken since that first guidance was issued.

So as mentioned, the administration has announced that the Public Health Emergency under 319 will end on May 11. As we've discussed before and as is noted in our FAQs on the website, we don't plan to take any action that would leave Americans without the tests that they need.

We recognize that the manufacturers of tests that were issued EUAs will need an appropriate period of transition time to transition to normal operations when the declaration under 564 is no longer in effect, but it is important to note that only the 319 is scheduled to end on May 11th. The 564 is separate and will continue until the HHS secretary terminates it. It is not dependent upon the 319 PHE declaration.

There's more information on our website in the FAQs about what happens when the 319 PHE expires, and we also have issued a draft guidance, last December, about the transition plan that is in the process of being finalized. And we received some great questions and comments during the comment period for the draft guidance, and those will be addressed in the final.

If you have specific questions about how to manage your current plans, you can always send an email to the EUA Templates mailbox or submit a Pre-Submission if you plan for a De Novo or 510(k).

And last update is a week or so ago, we made an update to our Understanding At-home OTC COVID-19 test page. This page has a step-by-step guide for lay users, and we updated that to include information about reporting OTC test results to the NIH-maintained website-- makemytestcount.org.

We do encourage test users to voluntarily and anonymously report their at-home COVID-19 test results. And users can report their results to that website-- makemytestcount.org-- or by using the reporting options that might be included with a test, such as some of the tests that have an app that includes a reporting options.

And with that, I can hand it back to Kim, and we can start the pre-submitted questions.

CDR Kim Piermatteo: Thank you, Toby, and thank you, Tim, for those remarks. We will now answer 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.

Alright, Toby, so we have one previously submitted question for mpox test development that we'll address today, and that question is, "As the cases of mpox in the US and worldwide have declined, will FDA consider revising the current requirements, such as reducing the number of samples required or extending the timelines, for the mpox EUA clinical studies, including those required as a condition of authorization when contrived specimens were used for the initial authorization?"

Toby Lowe: Thanks, Kim. So we do continue to monitor and assess the testing landscape in the United States and other relevant factors regarding the mpox outbreak, and we will revise policies and recommendations as appropriate. Since fresh mpox samples are unlikely to be available at any time in the near future, we suggest that those developers, who have validated their tests only on contrived samples, validate them on banked positives and negatives if they have not done so already.

And if a developer has further questions regarding their post-authorization study design, we recommend that you reach out to your FDA lead reviewer.

CDR Kim Piermatteo: Thanks, Toby. Now, we will move to address the previously emailed questions related to COVID-19 test development. And Toby, our first question is, "Does the FDA plan to publish recommendations for submissions of a flu/COVID-19 combination self-test?"

Toby Lowe: Thanks, Kim. So we have authorized several molecular and antigen, multi-analyte diagnostic tests intended for use at laboratory and point-of-care sites. Those, obviously, are different than an at-home or self-test, but we did grant full marketing authorization for the BIOFIRE Respiratory 2.1 Panel through the De Novo pathway, and we recently cleared the BIOFIRE SPOTFIRE Respiratory Panel through the dual 510(k) and CLIA waiver pathway, issuing a CLIA waiver at the same time as the clearance.

There is information in those review summaries or decision summaries, rather, that may be helpful for developers of multi-analyte tests. We haven't, obviously, issued or authorized, rather, any multi-analyte over-the-counter tests yet, but we do recognize the importance of such tests. And we recommend that developers follow the current recommendations in the molecular and antigen home-use template along with any relevant recommendations in the main molecular or antigen templates, depending on the particular test.

And as we've discussed here before, if you are considering an over-the-counter multi-analyte test, we recommend that you reach out to us for discussion. You can submit a pre-EUA or a Pre-Submission if you're pursuing a traditional marketing pathway, such as 510(k) or De Novo, to further discuss your test design and clinical validation proposal.

CDR Kim Piermatteo: Thanks, Toby. Alright, our next question is, "The molecular diagnostic home specimen collection template describes shipment stability testing recommendations. Can test developers use these recommendations to support a 510(k) submission?"

Toby Lowe: So it may be acceptable to use those shipping stability recommendations. However, the validation for a 510(k) is typically, more substantial than for an EUA. Developers can also take a look at the FDA-recognized CLSI standard EP25-A, which discusses suitability of IVD reagents. And we do generally recommend that developers submit a Pre-Submission or Q-Submission with their proposal for a COVID-19 test ahead of a 510(k) so that we can provide appropriate feedback for your particular situation.

CDR Kim Piermatteo: Thanks, Toby. Next question is, "Are separate EUAs required for an at-home collection kit and the assay with which the home collection kit will be used?"

Toby Lowe: So both the home collection kit and the assay do need to be authorized prior to being offered. As discussed in the Molecular Diagnostic Home Specimen Collection Template, there are three general options for how to seek authorization for an at-home collection kit for use with an assay. The home collection kit can be included as part of a single EUA request for a SARS-COV-2 molecular diagnostic test.

This would be appropriate generally, when the developer-- when the same developer is responsible for both the home collection kit and the molecular diagnostic test, and they're seeking authorization at the same time for that combination, of the assay and the collection kit.

The second option is multiple EUA requests. This is generally, appropriate when the developer of the home collection kit is different from the developer of the molecular diagnostic assay. So they would submit separate multiple or separate EUA requests and reference each other. And then, lastly, you could have a supplemental EUA request to an EUA of a previously authorized molecular diagnostic test to add a home collection-- to add home collection with a specific home collection kit.

CDR Kim Piermatteo: Thanks, Toby. So another question that we've received is, "What RT-PCR method does FDA recommend to confirm negative natural clinical matrix to be used for analytical studies? Do you require a 510(k) cleared or an EUA authorized RT-PCR SARS-COV-2 RT-PCR test?

Toby Lowe: Thanks, Kim. We do recommend that a developer confirm negative natural clinical matrix using either the candidate test or a 510(k) cleared or EUA authorized device. And generally, it is recommended to confirm with FDA that your selection is acceptable through the Pre-Sub process.

CDR Kim Piermatteo: Great. Thanks, Toby. So our last COVID-19 test development question previously submitted for today is, and it has several parts related to the impact of the Make My Test Count initiative. So first, how does the new makemytestcount.org initiative impact the utilization of existing app-based reporting functions and over-the-counter antigen tests? Secondly, should Make My Test

Count be offered as an alternative? And lastly, should users be cautioned not to submit results to both Make My Test Count and the rapid test's built-in reporting feature?

Toby Lowe: Thanks Kim. We do recommend that test users be cautioned not to report their test result more than once. Test users should report their COVID-19 test results to makemytestcount.org or use an app or other digital option for self-reporting that may be included with the test. We encourage the reporting of all results, including both negative and positive results, through the method included in an authorized test IFU or via makemytestcount.org, but they should not be reported through both for the same test.

CDR Kim Piermatteo: Thank you very much, Toby, for all of those responses. So that wraps up the previously emailed questions for both mpox and COVID-19 test development. We will now take 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 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.

Our first live question is coming from Josh. Josh, I have unmuted your line. Please, unmute yourself and ask your question. Josh, are you able to unmute your line?

Alright, we're going to go ahead and move on to the next stakeholder. That is Ali. Ali, I have unmuted your line. Please, unmute yourself and ask your question.

Ali Ghavanini: Thank you for the presentation today. This is Gabbiadini in Canada. I'm interested or curious to know, if there's any plan with the FDA to mandate having the Medical Device Single Audit Program-- MDSAP-- for the approval of the COVID tests since it looks like Canada has initiated or has the future plan to do that. Is there any plan for FDA to do the same as well? To manage--because I know that-- excuse me. I know that it's beneficial for auditing procedures, but for FDA, it's not a mandatory certification.

Timothy Stenzel: Yes, it's not mandatory in the United States. We do encourage it, and it is an available option where available for the US. So thank you for that question, and we'll record that request, I think, and consider it. Thank you.

Ali Ghavanini: So there are no near future plans for it, right, with the FDA?

Timothy Stenzel: Not to my knowledge, but this is a little bit off topic from COVID and mpox so just trying to be helpful there, but--

Ali Ghavanini: Thank you.

Timothy Stenzel: OK.

CDR Kim Piermatteo: Thanks, Tim, and thanks, Ali. Alright, our next question is coming from Michaela. Michaela, I unmuted your line. Please, limit yourself and ask your question.

Michaela Hoffmeyer: Hi, this is Michaela with TEIVD Solutions. I wanted to ask a question about flu samples for COVID-flu multiplex panels, whether they be molecular or antigen. So given that the flu season seems to be winding down, in the past, in full clearance submissions, the FDA has accepted maybe up to 30% OCONUS samples. We wanted to see, in light of the flu season winding down in the United States, if the agency would be willing to accept more samples from, say, the Southern hemisphere. Thank you.

Timothy Stenzel: Yes. In general, whenever-- and even for COVID, when COVID rates were very low at some points, we had opened up the possibility. For over-the-counter, there are important considerations for going in the Southern hemisphere. It's important that the speakers either speak English and understand written English and/or Spanish, if that's what's in the labeling, and that they not be provided instructions in their native language if it's other than Spanish or English. And this is because we won't want to test the test in the way that they would be used in the United States.

And there are certain considerations around, say, point-of-care testing outside the US, that it really reflect how the US that is performed by non-laboratorians. We have seen some sponsors not understand that and say something's point-of-care, when it's tested by trained laboratorians.

So the best thing to do is to submit a pre-EUA to do this. Also, there is relative openness for molecular assays for at least point-of-care to use bank samples when certain other analytes are in poor and very low-- when positives are very low for certain analytes other than COVID. COVID still, unfortunately, remains relatively prevalent in the US right now. Hopefully, that's helpful to you.

Michaela Hoffmeyer: Yes, thank you very much.

CDR Kim Piermatteo: Thank you. Alright. We're going to go ahead and move on to our next caller. Our next caller is Jon. I have unmuted your line. Please, unmute yourself and ask your question.

Jon: Hi, this is Jon Gould with McKesson. So I understand that COVID-19 vaccines are available for free to everyone six months or older living in the US, regardless of immigration or insurance status. When the COVID-19 pandemic is set to be over in May, will that remain or will the public have to pay for those vaccines?

Timothy Stenzel: Yeah, so this is an IVD call, not a vaccine call, and in any case that would not be a determination, to my knowledge, by the FDA, but I would refer you to the Department of HHS.

Jon: Thank you.

CDR Kim Piermatteo: Thanks, Tim. Alright, our next caller is Eric. Eric-- oops. I apologize. Eric, I'm going to come back to you. Homer, I've unmuted your line. Homer, if you can unmute, that would be great. Ask your question.

Homer Wu: OK. This is Homer from Hopkins MedTech Compliance. I have a question regarding to mpox. I know we still accept EUA, but if we decide to go to 510(k) premarket clearance, can we use the CDC orthopox virus-- the assay-- use that as predictor?

Timothy Stenzel: Yeah, so—

Homer Wu: Sorry.

Timothy Stenzel: Yeah, so the predicate assay would be anything that's FDA cleared, and the CDC assay is cleared. As far as the comparator goes, we generally, for these kinds of tests, have allowed either the FDA cleared or EUA authorized tests. The best way to pursue this is, I would recommend that you go and submit a Pre-Sub or Q-Sub for an IVD submission for mpox.

One of the big challenges right now is that there are, fortunately, so few fresh samples so that's typically needed for a full authorization submission. So unless somebody has already collected prospective fresh samples in an appropriate clinical study, it may be very challenging, which is why there are currently no plans to end the 564 for mpox, given that additional test development and finalizing test development for a full submission would be rather challenging.

Homer Wu: OK. Alright, thank you.

CDR Kim Piermatteo: Thank you, Homer, and thank you, Tim, for that response. Alright. Eric, I'm going to come back to you. I have unmuted your line. Please, unmute yourself and ask your question.

Eric Chen: No, thank you for that. I'm just making sure you guys can hear ok. So thanks, as always, to the FDA-- and this is Eric from Abbott Medical. So thanks always ways for the FDA in trying to be transparent and then having these town halls. I think it's very helpful for this. And it was more of a question for the team is, obviously, you've indicated that the PHS termination is going to be in May, and that has no effect on the EUAs, and that the next step will be, obviously, the HHS secretary is going to determine the appropriate time point that FDA and HHS think the EUA should end.

I'm curious, if you have any insights that you can provide to us and the audience today about, what process will FDA/HHS go through, and has there already been any discussions about when the 563 may come to an end? Do you believe that it might be this year or do you think it's going to be sometime in 2024? So you may not have these answers, but I was just curious, if there's any insights that you could provide the team or provide us.

Timothy Stenzel: Yeah, so--

Toby Lowe: Thanks, Eric. Sorry. Go ahead, Tim.

Timothy Stenzel: Maybe, I can start Toby, and then if I'm missing anything or if I speak incorrectly. I mean, our first goal is to make sure that the tests remain available. So along those lines, we have published a draft guidance for a transition period for when and if a 564 for COVID would end and what that would mean for developers.

It's envisioned that we would give developers time to get in a submission-- a full authorization submission, and it's envisioned that in a likelihood that-- it all depends on the final guidance wording, but as long as the submission is in by the deadline and the FDA continues to review that submission and there is nothing wrong with that submission, then that test can remain on the market.

So overall, the most important thing is that the tests remain available. It would be quite obvious for the FDA to take a look at how many full authorizations, De Novos granted, or tests cleared have been finalized and authorized by the FDA as a factor involved here. So we are continuing to encourage developers to come in as soon as possible with their full submissions if they wish to remain on the market for the long-term, which I do believe is a very important thing to do.

Toby, perhaps, you have some additional comments to make.

Toby Lowe: Thanks, Tim. I would just add that the draft guidance does lay out that we are contemplating and expecting a 180-day advanced notice for when the 564 will be terminated. So obviously, that notice-- the 180-day notice has not happened, yet. So that at least gives you an anticipated timeline and runway there. The guidance is in the process of being finalized, and when it is finalized, there will be a webinar on the final guidance, as we often do for final guidances.

Timothy Stenzel: Yeah. So there will be plenty of good communication, and we'll try not to surprise anybody out there. And again, most important thing is that test availability continue for COVID.

CDR Kim Piermatteo: Great. Thank you, Eric, and thank you, Tim and Toby, for those responses. Our next question is coming from Y-U-E-X-I-N-G. YueXing, I've unmuted your line. Please, unmute yourself and ask your question.

YueXing: Hi, this is Yue from Wondfo USA, and we have a question regarding flu A/B antigen test. This question is about the RT-PCR comparator method used in the clinical studies. So our CRO recommends us to use RT-PCR, which use a nasal swab sample type since our antigen test also collects nasal swabs.

Then, the methods will be narrowed down to Cepheid and Lyra flu A/B test. However, Cepheid is not manufacturing the flu test at this time, so does the FDA agree us to use the Lyra as the comparative method or we need to turn to other RT-PCR methods using nasopharyngeal swab sample types? Thanks a lot.

Timothy Stenzel: So I think, I'll turn this over to Kris to respond for this.

Kristian Roth: Sure, yeah. Thanks, Tim. So first thing, I think you want to ask us in a Pre-Submission an acceptable comparative method. So we are open to other sample types that potentially may not be the cleared sample type or a 510(k) cleared test. There's opportunity to perhaps do an analytical validation between sample types and just show that you're getting the same analytical sensitivity. So you can do that nasal swab to nasal swab comparison that you're perhaps, looking for.

I'm not sure if the Cepheid test you're talking about still has production challenges. I think we've heard other information from other sources so you may want to re-check with them, regarding the availability of that test.

YueXing: OK. So do you recommend us to use Lyra as well?

Kristian Roth: Again, I would just pose that question to us in a Pre-Submission. I believe, Lyra is an acceptable comparator method, but you would want to have that in writing from us prior to of starting your studies.

YueXing: OK. Thank you so much.

Kristian Roth: Thank you.

Timothy Stenzel: And one of the reasons that we hesitate to confirm specific manufacturers or test developers for a comparator is we do believe that test developers have freedom to choose the comparator they wish, but we do want to have you make sure.

And we're really not wanting to highlight only a subset of potential manufacturers on this call and in this public forum. So that's typically, why we want to handle that one-on-one offline, and understand what comparator you would like to use and be able to respond to you in that way. Thank you.

YueXing: Thank you so much.

CDR Kim Piermatteo: Thank you, everyone. Alright, our next question is coming from MBeckman. I have unmuted your line. Please, unmute yourself and ask your question.

MBeckman: OK. Can you hear me?

CDR Kim Piermatteo: Yes, we can.

MBeckman: If we're preparing an assay for 510(k) approval post—the EUA stuff, is the platform that we're going to run the assay on as critical as the assay itself, in terms of FDA requirements and stuff like that, or can we choose a platform that we know works and has worked well through the pandemic and then develop the assay as the 510(k) piece?

Timothy Stenzel: Yeah, so that's a multifaceted-- the answer will be multifaceted, and it may depend on the design and function of your particular assay reagents. So typically, we allow manufacturers or developers to choose, with their assay, how they set that up and what instrument or instruments they choose to have that.

For those developers that develop a kit that would be distributed, it's frequently important, but not always absolutely necessary-- but typically, it's thought to be highly good to develop your test on an FDA platform, that's our instrument that's made under GMP.

And that is, it doesn't have to have been brought into the FDA before. It can be the first time. But if it's not made under GMP, then there are a whole host of questions and responsibilities that a test developer would have to take on if it's not made under GMP, so we do recommend basically, IVD grade instruments.

The important elements of a test include not just a performing, say, PCR but also the readouts in any software. So this is probably, best handled through a Q-Sub/Pre-Sub to the office, and we are accepting those, and we are trying to turn those around quickly for-- we are getting back to our stated MDUFA-- MDUFA V now, for new submissions, MDUFA V turnaround times on submission. So that is our goal.

MBeckman: OK, thank you.

Timothy Stenzel: Um-hum.

CDR Kim Piermatteo: Thank you for that question, and thank you, Tim. Alright. At this time, I'm going to make a call out, if anyone has any more questions, to please raise your hand.

Alright, I do not see any more raised hands for today, so we're going to go ahead and move to close today's town hall. I want to thank our panelists today-- Tim, Toby, Kris, and Noel-- for their responses to our questions, as well as thank you to everyone for your participation.

Today's virtual 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.

And as a reminder, if you have any additional questions about mpox test development, you may send an email to MPXDx@fda.hhs.gov and for any additional questions about COVID-19 test development, you may send an email to COVID19DX@fda.hhs.gov.

As a reminder, our next and last regularly scheduled virtual town hall will be for mpox and COVID-19 test developers on Wednesday, March 22, 2023 from 12:05 to 1:00 PM Eastern time.

This concludes today's virtual town hall, thank you all for joining us, and have a great day.

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