

**Virtual Town Hall Series - Monkeypox Test Development and Validation
September 21, 2022**

Moderator: Joseph Tartal

Joseph Tartal: Hello, and welcome everyone, to today's Virtual IVD Town Hall for Monkeypox Test Developers in which we'll discuss and answer your questions about diagnostic tests in response to the monkeypox public health emergency. Thank you for joining us today. I'm Joseph Tartal, Deputy Director in the Division of Industry and Consumer Education in CDRH's Office of Communication and Education. And I will be your moderator for today's town hall.

Our panelists for today's town hall are Dr. Timothy Stenzel, Director of the Office of In Vitro Diagnostics, which is also referred to as the Office of Health Technology number 7 or OHT7 in CDRH's Office of Product Evaluation and Quality, or OPEQ. Toby Lowe, Associate Director for Regulatory Programs in OHT7. And Dr. Kristian Roth, Deputy Director of the Division of Microbiology Devices, also in OHT7.

For today's town hall, we'll begin with Toby providing opening remarks, followed by answering your previously emailed questions and then we will proceed to address your live questions. A recording of today's town hall and transcript will be made available on CDRH Learn under the section title "Specialty Technical Topics," and then the subsection title "Public Health Emergencies." A recording and transcript of last week's webinar on the policy for monkeypox tests has been posted.

We will continue holding these town halls weekly, every Wednesday. Therefore, the next scheduled IVD Town Hall will be on Wednesday, September 28, 2022, from 12:05 to 1:00 PM Eastern Standard Time. This will be a combined town hall for both topics of monkeypox and COVID test developers. We will then hold town halls on October 5th and October 12th for monkeypox test developers specifically.

Future dates for town halls will be announced once they have been confirmed. Please refer to our Medical Device Webinars and Stakeholders Call webpage for details on upcoming IVD Town Halls. A link to this web page has been provided on the bottom of this slide.

And lastly, I have one administrative reminder. For those of you participating live in today's town hall, please be sure you have joined the town hall via the Zoom app and not through a web browser to avoid any technical issues.

I'd now like to welcome Toby, who will provide today's opening remarks on important dates. Toby, the floor is yours.

Toby Lowe: Thanks, Joe. And hi everyone. Thanks for joining us again. So we just wanted to go over the dates that are noted in the guidance that we thought test developers should be well aware of. So October 13, 2022 is 30 days after the publication of the notice of availability of the guidance. So the guidance posted on our website on October-- I'm sorry, on September 7th. But the notice of availability published in the Federal Register on September 13. So 30 days after that is October 13.

And that is important for the policies both in section IV.A.1 and IV.A.2. So for the prioritization of review of EUA requests, the guidance notes that we will intend to prioritize tests from developers that inform FDA of their intent to submit an EUA request within 30 days after publication of the notice of availability of the guidance.

And then for Section IV.A.2, which talks about the notification to FDA for certain diagnostic tests developed and performed by laboratories, we intend to accept notifications within that same 30 days. And we ask that laboratories notify FDA within five business days of offering their test that the lab has appropriately validated the test. And in most cases, we do not intend to object to the laboratory offering that test for clinical use without an EUA request, without submitting any EUA request.

And those intent to submit and the notifications can be sent to the MPXDx@fda.hhs.gov mailbox, where you can also send any questions that you may have.

Joseph Tartal: OK, thank you Toby, for those remarks.

We'll now answer your previously emailed questions. Please note we do receive some questions that are too detailed or too test case specific that we will not address today. For those questions, we'll try to send a response in writing within a few days. If you 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 for an update.

Toby, I'll be directing these questions to you. And the first question is, what FDA cleared or authorized monkeypox tests are available?

Toby Lowe: Thanks, Joe. So the Centers for Disease Control and Prevention, CDC, Non-variola Orthopoxvirus Real-Time PCR Primer and Probe Set is the only monkeypox test that is currently FDA cleared through the 510(k) regulatory pathway. It is a real time PCR test that detects non-variola Orthopoxvirus DNA, including monkeypox virus. And the CDC test is available in designated CDC Laboratory Response Network laboratories and other CDC designated laboratories, which at this point are LabCorp, Quest, Mayo, Aegis, and Sonic.

Additionally, there is currently one test that has received an EUA. That's the Quest Diagnostics Monkeypox Virus Qualitative Real-time PCR Assay. And that detects DNA from the monkeypox virus, clade II, or the West African clade, and non-variola Orthopoxvirus.

Joseph Tartal: Thank you. And what test is detected by the Quest Diagnostic Monkeypox Virus Qualitative Real-Time PCR assay?

Toby Lowe: So I think that's what target is detected by that assay. And the Quest Monkeypox Virus assay targets both non-variola Orthopoxvirus and monkeypox virus. The non-variola Orthopoxvirus target detects a region of Orthopoxvirus DNA polymerase gene E9L, which detects several members of the Orthopoxvirus genus, including monkeypox, vaccinia, and ectromelia viruses.

And then the monkeypox target detects a region of the monkeypox virus, clade II, the TNF gene, or the Tumor Necrosis Factor receptor gene. There's also additional information on the Quest assay in the EUA summary that's posted on FDA'S EUA Monkeypox page.

Joseph Tartal: OK, thank you on both those answers with regards to available tests. Our next question has to do with sampling. Is there any evidence of whole blood sample detection and its consideration for sampling for monkeypox tests?

Toby Lowe: We're not aware of any other validated specimen types for diagnosing monkeypox at this time, other than lesion swab samples. And so currently, the recommended specimen type is skin lesion material. We have the most experience with this sample type and it has generally been performing well in the current outbreak. We encourage any test developers that are interested in claiming non-conventional sample types to submit a pre-EUA to obtain feedback on their proposed analytical and clinical study designs.

Joseph Tartal: OK, thank you for that answer on samples. The next question is actually a three-part question. And I'll do each part individually. So the first part is, when will FDA publish a template for monkeypox rapid tests?

Toby Lowe: We did discuss this briefly in the previous monkeypox webinar last week. We are working on a rapid antigen template and will provide that as soon as possible. In the meantime, we encourage interested test developers to apply to the NIH Monkeypox ITAP program, which NIH announced last week. And they have already begun accepting applications.

Joseph Tartal: OK, thank you. The next part is, will FDA consider over-the-counter use for monkeypox rapid tests?

Toby Lowe: So we are continuing to consider the ongoing testing needs to address the public health needs and increase the availability of tests that will have the biggest impact on the nation's ongoing monkeypox outbreak. And we encourage test developers that are interested in over-the-counter monkeypox rapid tests to apply to the NIH Monkeypox ITAP program. And you can also submit a pre-EUA to discuss any of your innovative proposals with FDA. And Tim, do you want to add anything on that one on over-the-counter?

Timothy Stenzel: Yeah. Hopefully, they can hear me. So we do encourage innovation. It may be that rapid antigen tests are not going to be sensitive enough for monkeypox. We don't know yet. Once we start getting applications for rapid antigen tests, we'll see. But we do know that molecular tests are sensitive enough.

And so, I think there is an area of innovation for over-the-counter tests on higher sensitivity rapid tests. Now, that may be molecular technology. We did authorize three OTC molecular tests for COVID. However, we do understand that those testing technologies right now are more expensive than rapid antigen tests in the home.

So one of the unmet needs for over-the-counter, and even for point of care, probably, are lower-cost molecular test options that have-- that bridge the gap between high-sensitivity molecular tests and lower-cost rapid antigen tests. So just throwing that out there. Thanks, Toby. Back over to you.

Joseph Tartal: OK. Thank you, Tim, and thank you, Toby. Our next question-- the next part of this question is what does FDA recommend using as a comparator for validation?

Toby Lowe: Thanks Tim and Joe. Alright, so we do have some discussion of comparators for validation in the templates. And importantly, the templates do note that at this time our initial validation recommendations are for clinical validation with contrived specimens. And if clinical samples become more widely available, we may revise this recommendation.

If you do have access to clinical samples, or want to pursue that option, we generally recommend using a high-sensitivity FDA cleared or EUA authorized RT-PCR assay, which uses a chemical lysis step, followed by solid phase extraction of nucleic acid, such as silica bead extraction as the comparator test. And it's important that comparator test be one that has been validated with clinical specimens.

At this point, the CDC cleared assay is the only one that meets that, but, hopefully, there will be additional options in the future. Since only certain laboratories may perform the currently cleared test, as well as authorized, you may consider reaching out to one of those laboratories using that test and they may be able to provide leftover samples that other developers can use for validation. And when doing that, they can usually provide the test results from the cleared or authorized test, along with the Ct values observed for each sample upon request.

And if you have any questions about choosing the appropriate comparator or are encountering difficulties accessing the comparator testing, you can reach out to FDA through the MPXDx mailbox. And Tim, did you want to add anything on this one?

Timothy Stenzel: No, I think that's great. Thanks, Toby.

Toby Lowe: Sure.

Joseph Tartal: OK, Thank you, guys. We'll go on to our next question. And this has more to do with our process. What happens after a test developer informs FDA of its intent to submit an emergency use authorization request?

Toby Lowe: Yeah, so when FDA receives an email from a developer informing FDA of the developer's intent to submit an EUA request, we will generally log that in as a pre-EUA. So then the developer would receive a response with a pre-EUA number for tracking purposes. Then FDA will consider the information that the developer provided regarding whether or not FDA would prioritize a future EUA request for that test.

After the FDA's consideration, FDA will respond back to the developer indicating whether or not FDA intends to prioritize a future EUA request if submitted for that test. We intend for that response to inform the developer's plans and decisions regarding whether to submit a future EUA request. And if we respond that we would not intend to prioritize review for the test, we do plan to include high-level reasons why, but it is important to note that it's not a substantive review of the test, so it won't include any deficiencies related to validation that may have been provided to the FDA in that email.

And then, of course, the full authorization pathways, such as 510(k), are also an option for developers.

Joseph Tartal: OK, thank you Toby. Our next question, and this kind of links back to your opening remarks, can test developers still submit an emergency use authorization request later if they do not inform FDA of their intent to submit an emergency use authorization within the 30-day window from when the guidance was issued?

Toby Lowe: Thanks Joe. So as discussed in the guidance and in my opening remarks, we do intend to prioritize review of EUA requests for certain types of monkeypox diagnostic tests, including those from manufacturers who inform FDA within 30 days after publication of the notice of availability of the

guidance in the Federal Register. We do plan to monitor the situation and may adjust the prioritization, including shortening or lengthening that time period as appropriate.

And importantly, developers may submit an EUA request at any time while a 564 declaration is in effect, which is discussed in the guidance. And as discussed in the guidance, we will consider-- FDA will consider whether or not to review and process that EUA request based on a variety of factors related to whether the action is necessary to protect the public health in an emergency.

Joseph Tartal: OK, very good. Thank you, Toby. We'll move to our next question. Can FDA clarify what you consider to be high throughput and high manufacturing capacity for monkeypox emergency use authorization review prioritization?

Toby Lowe: Yeah, so as we stated in the guidance document, we do plan to prioritize review of requests of high throughput diagnostic tests from experienced developers with high manufacturing capacity where authorization would significantly increase testing capacity to address public health needs. Since these are two of several factors considered for prioritization, and as we noted in the guidance, we recommend that developers send information, including their test throughput manufacturing capacity and the other information noted in the guidance to FDA indicating their intent to submit an EUA request for a monkeypox diagnostic test. And we intend to respond, noting whether FDA intends to prioritize review of the proposed test.

And so as we've discussed previously, that information can be sent by email to MPXDx@fda.hhs.gov with the subject line "Diagnostic Test for Monkeypox – Intent to Submit EUA Request - Test Summary Information."

Joseph Tartal: Thank you. And we'll move on to our next question. This has to do with getting hold of a comparator. Can FDA clarify how test developers can obtain the FDA cleared CDC non-variola Orthopoxvirus test from CDC to use as a comparator test?

Toby Lowe: Yeah, so this goes back to the previous question. And I believe we also discussed this on the town hall last week. Since only laboratories that are designated by the CDC may perform the FDA cleared CDC test, we recommend that you reach out to one of those laboratories for assistance with that. And those laboratories may be able to provide leftover samples to use for validation. And they can provide that with the CDC test results and the Ct values observed for each sample.

But also, as we've discussed, initial validation can be done on contrived samples and you can also reach out to FDA at MPXDx@fda.hhs.gov if you have difficulty accessing comparator testing.

Joseph Tartal: Thank you, Toby. And this actually was the last question that was pre-sent and wraps up the previously submitted questions portion of our town hall today.

So we'll now take your live questions. To ask a live questions, 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 additional questions, you may raise your hand again to get back into the queue and then I will call on you as time permits.

So with that, let's get to the first question. Wenli, I'm going to unmute your line. Now, please unmute yourself and ask your question.

Wenli Zhou: Thank you very much. This is Wenli Zhou from XYZ Laboratory. And yeah, I have a question here. I realize from the policy that the FDA is doing, the [INAUDIBLE – priority or early] review for the submission, the FDA notification submission. So I'm just wondering how long is it taking to get a response from the FDA now for the manufacturer to know if their project is a prioritized or not?

Timothy Stenzel: So, typically, we can do a pretty quick review of that. But we may, in some cases, want to see all of the submissions that we get for interest and test development through the open window for that before we make final decisions. So we'll get back to you as soon as possible. And we'll get back to you certainly, if not within that 30-day window, shortly thereafter.

Wenli Zhou: OK, thank you very much.

Joseph Tartal: Alright, let's go to our next question, which is from Jennifer. Jennifer, I'm unmuting your line. Please unmute yourself and ask your question.

Jennifer Stanford: Thank you very much. This is Jennifer Stanford from Hopkins MedTech Compliance. And I have a question regarding if we would like to try to do a retrospective enrollment study with patients who have already been diagnosed and bringing them back in. That was one of the options in the guidelines. If we did that, would we be able to use one sample, such as if we collect one lesion sample with a 3 mil VTM solution, to use to test both the investigational PCR test as well as the comparator? Or do we need to do two separate swabs from the same lesion?

And the reason I ask is because you might actually do the swab in a slightly different location in that same lesion and potentially have different viral loads. So we were just trying to figure out what would be the best methodology for that.

Timothy Stenzel: Yeah, I think that if you're concerned about consistent swabbing from a lesion, because the FDA will allow transport media that's been validated for an amp assay in a submission, that as long as the comparator test allows that same VTM you can, perhaps, split the sample. You want to make sure that the comparator test has enough volume and you can communicate with whoever is doing that testing to make sure that that's going to be sufficient.

Right now, the only comparator test available is the FDA cleared CDC assay run at the LRN Labs and the five major reference labs that are testing with it. The CDC has requested that we don't send repeat, any sort of repeat testing, where a patient's already been diagnosed in, because that would utilize additional kit reagents. And they're trying to manage that and meet the response needs.

So obtaining a residual sample material from any of the LRN Labs or any of the five reference labs that are testing with the CDC-- FDA cleared kit is probably one of the best options for your device, as long as those kind of samples are acceptable to you. That way, you get what you need. It probably is easier to do.

It can be retrospective. We are going to look at things like were possible consecutive samples selected from those resources from those labs? And we'll want to know if there's any gaps and why there are

gaps in those consecutive series of samples, so that there is a limitation on any sort of bias. Hopefully, that addresses your question.

As we authorize additional tests that have been validated with actual patient samples, then there will be more comparator tests available.

Jennifer Stanford: OK, so just to clarify, it sounds like you're not encouraging us to do the retrospective model, where we would take patients who've already been diagnosed and bring them back in for retesting, simply because of the shortage of reagents and we already know they're positive. So you would rather us use contrived samples for this testing.

Timothy Stenzel: Yeah, if you can't easily obtain actual patient samples then a contrived is a better route to take right now because of the availability of the CDC test for this prospective, retrospective look that you're talking about. Because if these patients have already been diagnosed, particularly with those CDC assay, then they don't need it for diagnosis. However, if the CDC assay-- if you're doing a study where the CDC assay is ordered as the test of record and the comparator is one in the same, then that would work if that's easier for you to use. But I think you're correct on your assessment. Thanks.

Jennifer Stanford: OK, thank you very much.

Joseph Tartal: Thank you for your question, Jennifer. And thank you Tim, for the response. Our next question is from Homer. Homer, I'm going to unmute your line. Please unmute yourself and ask your question.

Homer Wu: Hi, this is Homer Wu from Hopkins MedTech Compliance. I have a separate question, which is, in the template we mentioned that we can use home collection kit. But there's no instruction on how we validate the home collection kit. Or can we just use like approved COVID-19 home collection kit?

Timothy Stenzel: So they may or may not be suitable, since this is a lesion swab versus another type of swab. And if it would involve something like saliva, then we would want to see, as mentioned earlier, that we'd want to see your plans for validating that. We are working on a home collection template. It wasn't ready to be released at the time of the guidance. And so we are working on that. And we will get that cleared and posted as soon as possible.

Homer Wu: OK, just follow up on this. Since we want to be the priority and that is one of the options, to do the home collection kit, so can we-- when we submit, can we claim that we're going to have a home collection kit, but—

Timothy Stenzel: Yeah, in the 30-day-- in the 30-day window, if you're a test developer and you want to develop something, then that can go in there that you want to develop a home collection kit. And we'll want to know what assay you're going to use with that home collection kit. And that can go into an email to the FDA and we can assess that, on whether or not we would invite you to submit an EUA. And then we'll work with you-- if we do invite you, we'll work with you going forward on how to do that validation.

Homer Wu: Alright, great thank you.

Toby Lowe: To add to what Tim was just saying, the 30 days is not to submit your EUA request. The 30 days is to inform us that you intend to submit an EUA request.

Homer Wu: This is Toby, right? So I do have a question. Based on the current template, if we can complete the performance in the lab and if we can perform the contrived sample, actually, according to the templates, then we can submit the EUA, right?

Timothy Stenzel: You can submit an EUA after you've said that you would like to and get a positive response from the FDA. That's how we're doing the prioritization for any kit manufacturers. So it is best before you do any validation to go ahead and make sure that we would prioritize your EUA when it does come in. So please go back to the guidance document and that can explain all these details. Thank you.

Homer Wu: Alright, thank you.

Joseph Tartal: OK, thank you. Our next question is from Om Singh. I'm unmuted your mic. Please unmute yourself and ask your question.

Om Singh: Thank you for the opportunity to ask the question. If a lab is certified with the CLIA and they have these validated testing and everything, do they still need to go through the EUA process in order to commercialize the kit?

Timothy Stenzel: So if you're talking about a lab developed test for a single site that is using PCR to test lesions, that individual lab just needs to have notified the FDA within the time periods that are spelled out in the guidance, and which Toby went over, again, at the top of the hour. If a developer is developing a kit, then it needs to be EUA authorized before it can be distributed.

Om Singh: OK, so a lab can do it individually, but if a developer, who's putting the kit in the market, need EUA certification. Am I getting it right?

Timothy Stenzel: Go ahead, Toby.

Toby Lowe: Yeah, so if you are a high-complexity CLIA certified laboratory, and you are developing your own test in-house, and using that test in-house at your single site, and it's a PCR test, lesion swab specimens-- all of the details for this are laid out in the guidance document-- then we ask that you notify us within five days of offering the test that you have appropriately validated the test. And we do not expect you to submit an EUA request.

If you are intending to distribute that test, whether it's-- whether you're considering it to be a kit or otherwise, we do expect that you submit an EUA request and get authorized prior to distributing any test.

Om Singh: Thank you, appreciate it.

Timothy Stenzel: Yeah, and Toby mentioned that the 30-day window for LDT notification of the FDA and kit manufacturer email, one, expressing interest in developing an EUA authorized test. That 30-day window closes on October 13.

OK, I think we can go to the next question.

Joseph Tartal: We'll move to the next question. Dennis, I'm going to open up your line. Please unmute yourself and ask your question.

Dennis Repella: Hi, Dennis Repella, Smith Associates, FDA consultants in Crofton, Maryland. What's the current estimate of how many of these monkeypox cases will be identified in the next 12 to 18 months?

Timothy Stenzel: The number of cases is that are being identified with sufficient testing in the United States is going down. It is now around a little bit over 200 cases a day and that's down from a high of probably more than double that in the U.S. In the world, the number of cases are going down as well. Currently, it's 600.

So we would love to see this outbreak end sooner than later. And if you were to just draw a straight line on what the curve is doing right now, the emergency may end sooner than later. But it's really hard to predict. The CDC has given guidance on how to limit the spread of the disease. They're getting that word out as best they can.

There are vaccines available to the high-risk populations that is going forward. And all of those efforts, combined with testing, hopefully will drive this response to a close in the U.S. sooner than later. But I cannot predict. I do not have a crystal ball. I don't know if our efforts will continue to have the success they have so far.

Dennis Repella: Well, thank you very much. I appreciate the answer.

Joseph Tartal: OK, with that, that was our last live question for today. Thank you everyone for your participation today. And I want to, again, thank our panelists, Tim, Toby, and Kris.

A recording of today's webinar and transcript will be posted to CDRH Learn under the section title "Specialty Technical Topics," and then the subsection titled "Public Health Emergencies." To access those materials, please visit CDRH Learn at the link provided on this slide.

For additional questions about today's town hall and monkeypox IVD topics in general, you may send an email to MPXDx@fda.hhs.gov.

Please remember to join us for the next IVD town hall for monkeypox and COVID test developers on Wednesday, September 28, 2022, from 12:05 to 1:00 PM Eastern time.

Thank you again for joining us. This concludes today's town hall. Have a nice day.

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