**CDRH Virtual Town Hall #94**
**Monkeypox Test Development and Validation**
**October 5, 2022**

**Joseph Tartal:** Hello and welcome everyone to today's Virtual Town Hall number 94. Today we will 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 Education, and I will be your moderator. Tim Stenzel and Toby Lowe are both on leave this week. Our panelists for today are Dr. Kristian Roth, Deputy Director of the Division of Microbiology Devices in the Office of In Vitro Diagnostics, which is also referred to as the Office of Health Technology number 7, or OHT7, in CDRH Office of Product Evaluation and Quality, or OPEQ; and Dr. Noel Gerald, Branch Chief for Bacterial Respiratory and Medical Countermeasures, also in OHT7.

For today's town hall we'll begin with opening remarks from Kris. Then we'll answer your previously emailed questions about monkeypox. And last, we'll address your live questions. The presentation slide and transcript of last week's combined monkeypox and COVID virtual town hall have been posted.

We will continue holding these virtual town halls weekly every Wednesday. The next virtual town hall is scheduled for Wednesday, October 12 from 12:05 to 1:00 PM Eastern time and will be for monkeypox test developers specifically. Future dates for virtual town halls will be announced once they have been confirmed.

Please refer to our “Medical Device Webinars and Stakeholder Calls” webpage, specifically, our “Virtual Town Hall Series - Test Development and Validation During Public Health Emergencies (COVID-19 and Monkeypox)” webpage for details on upcoming virtual town halls town halls.

I would also like to provide you an update on where to find information from past town halls. Last week's virtual town hall materials have been posted to the table on the “Virtual Town Hall Series - Test Development and Validation During Public Health Emergencies (COVID-19 and Monkeypox)” webpage under the section “Previous Town Halls for Test Development and Validation During Public Health Emergencies.” Links to these web pages are provided on the bottom of this slide.

And last, as a friendly reminder for those of you participating live in today's town hall, please be sure to join the town hall via the Zoom app and not through a web browser to avoid any technical issues.

I now would like to welcome Kris, who will provide today's opening remarks. Kris, the floor is yours.

**Kristian Roth:** OK, great. Thank you, Joe. I just want to remind everyone of an important date that is coming up quickly. October 13, 2022 is the 30-day mark after publication of the monkeypox test policy guidance. This is the deadline for LDT notifications to be sent to FDA and for experienced developers to inform FDA by email of their intent to submit an EUA request for monkeypox diagnostic tests. So please, do keep that in mind. October 13 is coming up.

We would also like to remind today's callers that the FDA does not expect an EUA request for certain validated monkeypox diagnostic LDTs. These are tests that are developed and performed in a single site,

high complexity, CLIA-certified lab and use PCR and region swab samples. FDA only expects a notification by email, with no data, no review, and no decision by the FDA, on an application and no issuance of an EUA as well. So this is just a notification to us of your practices that are going on in your laboratory.

Outside of a declared emergency and prior to the EUA test declaration for monkeypox, the FDA generally has exercised enforcement discretion for single-site laboratories, or more commonly referred to as LDTs. And for the subset of monkeypox diagnostic LDTs, the FDA also implemented a narrow policy of enforcement discretion after the EUA test declaration for monkeypox. Again, this is all covered in the guidance, which is linked to this presentation. And you can see that for more details.

And that's it, Joe. Thank you.

**Joseph Tartal:** OK. Thank you, Kris, for those opening remarks. We'll now answer your previously emailed questions. Please note that 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 for an update.

And with that, we will now get to those previously emailed questions.

So Kris, I'll be directing this first question to you. Can FDA clarify if it is acceptable to validate a monkeypox point-of-care test using contrived samples?

**Kristian Roth:** Yeah. Thanks, Joe. For tests intended for a point-of-care setting, or POC setting, it is important to demonstrate that non-laboratory health care providers can properly perform the test accurately in the intended use environment and to ensure that the test is reliable and reproducible, combined with potentially uncontrolled environments. The clinical study should mimic how the test will be used in real life, including validated with natural positive clinical samples.

As stated in the template for developers of molecular tests for monkeypox, the FDA generally recommends that 30 prospectively collected positive-- and positive would be confirmed by EUA authorized or cleared test-- and 30 negative natural clinical specimens be tested. Mock clinical samples are not appropriate for this POC clinical study. If obtaining positive specimens is challenging, you may be able to collect samples in another site and ship to a testing site, or potentially use bank samples to supplement your positive specimens. I would recommend you refer to the molecular monkeypox template for additional recommendations on the use of banked natural clinical samples, which are appropriate to support a point-of-care claim.

We note that contrived samples can be evaluated in a separate study to demonstrate test performance with low positive samples around a LoD. However, these samples are intended to supplement, not replace the natural clinical samples in your clinical study. And at this time, I'd like to ask Noel if there's any other information you'd like to provide on this question.

**Noel Gerald:** Thanks, Kris. No, I think you captured it. For point of care, we are expecting to see natural clinical study sample testing and that any contrived samples for LoD is a separate analysis. And they don't replace the clinical study tests.

**Kristian Roth:** Great. Thanks so much. Alright, back to you, Joe.

**Joseph Tartal:** OK. Thank you, Kris. Thank you, Noel. So our next question is actually a couple questions broken down. And I'll start with the first one for you, Kris. Will there be a demand for single target products?

**Kristian Roth:** Thank you. As a performance of a diagnostic test can be impacted by viral mutation, FDA encourages developers to design their tests to minimize the impact of viral mutations on test performance. For instance, CDC has recently reported observing a gene deletion in some monkeypox samples from California. This impacts some of the previously published primer and probe sequences that some organizations are planning to incorporate into their tests.

This is kind of the first instance that we've seen of potential variation in the monkeypox genome. And we will continue to monitor for these variations and the impact that they have on diagnostic tests. Because of situations like this, FDA recommends including a highly conserved monkeypox virus target-- for example, a target in a portion of the genetic code not restricted to a specific monkeypox virus variant-- or non-variola orthopox target-- a non-variola orthopox target as part of a multiple target test, which may improve performance with new genetic variants. However, the number of targets in the test should be appropriate to provide resilience.

By resilience, I think we mean a reduction of the risk that viral mutation impact test performance-- this, coupled with the efficiently leveraging developer and laboratory resources. So typically, if you have more than one-- two to four targets-- that's generally a good number to shoot for, which maximizes, again, efficiency in resources and again providing that resilience to viral mutation. That's it. Back to you, Joe.

**Joseph Tartal:** Thank you. And this next question is the last of our written-in questions for the day and builds off of that. Is it acceptable for the clinical comparison method to be Sanger sequenced?

**Kristian Roth:** Thanks. As noted in the molecular diagnostic templates, at this time the FDA's initial validation recommendations are for clinical validation with contrived specimens for laboratory tests run on lesion swab samples. If clinical samples become more widely available, the FDA may revise this recommendation. Since only certain labs may perform the FDA-cleared test, you may consider reaching out to one of these laboratories.

These labs may provide leftover samples that other developers can use for validation. In doing so, they can provide the test results from the cleared tests, along with the Ct values observed for each sample upon request. I was wondering, Noel, do you have any comments you'd like to add?

**Noel Gerald**: No, I think that covers it.

**Kristian Roth:** OK. If you do have questions about choosing appropriate comparator specific to your assay or situation or are encountering difficulties, you can always reach out to the MPXDx@fda.hhs.gov email address.

**Joseph Tartal:** Thank you, Kris. And that wraps up the previously emailed questions for today. We will now move to your live questions.

And to ask a live question, please select the Raise Hand icon at the bottom of your Zoom screen. When you're 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'll call on you as time permits.

So far, we do not have any live questions. If anyone wants to ask a live question-- oh, we do. So there we go. Zahra, I'm going to unmute you. Please unmute yourself and ask your question.

**Zahra Lakhani:** Hi, I'm in Richmond, Virginia. I have a suggestion, more than a question. This information is very vital and very productive. And everyone must have access, especially the families who has children going to school with children with special needs, and even for general public. Are there any possibilities that school can also invite-- I mean, I just happen to know this seminar. But then if some way of school happened to have these things and somewhere we can put it on their website, so parents, they can stay up on top of everything. Yeah. Just a suggestion.

**Kristian Roth:** Yeah, thanks for that. I might take that back to Joe for a answer.

**Joseph Tartal:** I mean, what I would recommend is the public pages for monkeypox, they're online. You can sort through them. If you have any general questions about finding these pages, you can always reach out to our division at Division of Industry and Consumer Education.

We have phone lines Monday through Friday that we can help link people up with those web pages. And we also have general emails that we can answer on general questions about monkeypox. And that email address is DICE@fda.hhs.gov.

For most of these town halls, they are promoted for the test developers. So it's more for those folks who are trying to develop tests. So thank you for your question.

Our next question is from Sarah. Sarah, I'm going to unmute your line. You're unmuted. Please unmute yourself and ask your question.

**Sarah Barchard:** Hi, good morning. My name is Sarah Barchard I'm calling from DCN Diagnostics. I have a client who's developing a monkeypox lateral flow immunoassay. And they had a question about the lysate for their analytical testing. Is there a lysate that you can recommend that they use that does not require a BSL-3 laboratory? They don't have access to one currently.

**Kristian Roth:** Yes, thanks. Noel, would you mind taking this one?

**Noel Gerald:** Sure. So when you say it's an immunoassay, I just want to clarify. So is this an antigen test?

**Sarah Barchard:** Yes, correct.

**Noel Gerald:** And then what is the setting that you're intending this for? This is for point-of-care?

**Sarah Barchard:** Yes, it's for point-of-care.

**Noel Gerald:** Yeah, so I'm just going to make sure that I understand the question. You're asking if we have specific recommendations for the composition of the lysate buffers that will be used. So there's a portion of the lysate that you think that would require BSL-3 to be separate from the organism?

**Sarah Barchard:** Yes. So I think the client mentioned that it's an inactivated lysate that's recommended.

**Kristian Roth:** So you're talking about test material. What test material can you acquire that is appropriate for your BSL setting?

**Noel Gerald:** Right. Yeah. So there's the test material like positive controls. So that might be inactivated viral material. And so then there are requirements around what types of viral materials you are including with your test, but not so much about just the strict lysate buffers themselves.

**Sarah Barchard:** OK. Thank you.

**Joseph Tartal:** OK. Thank you, Sarah. Our next question is from Samuel. Samuel, I'm going to unmute your line. Please unmute yourself and ask your question.

**Samuel Reichberg:** Yes, Sam Reichberg from Pandemic Response Lab in New York. I want to ask a question about what additional requirements, other than the notification, is needed for laboratory developed test that is tested, developed, and offered by a single lab?

**Kristian Roth:** Right. Thank you. Go ahead.

**Samuel Reichberg:** Yeah. Namely, is EUA required subsequently or some other requirement?

**Kristian Roth:** Great. Thanks. I think at this time, we're just asking for notification. And if your test is a PCR test from a lesion swab sample, then it is appropriate for that notification pathway. If you're doing other types of testing, such as home testing, saliva testing, things that are kind of outside that narrow scope, the pathway is a little bit different. But again, if you're doing that PCR from lesion swab samples, that is really what that notification pathway was intended for.

**Samuel Reichberg:** Thank you.

**Joseph Tartal:** OK. Thank you for your question. And North, I'm unmuting your line. Please unmute yourself and ask your question.

**Leslie North:** Yeah. Hi, this is Leslie North. I'm in Portland, Oregon. I did have a question with regards to the clinical studies. I assume that once manufacturers start our efforts on these clinical studies, there's going to be a lot of competition to work with the labs that are involved in the Laboratory Response Network. So I was wondering whether or not FDA would consider working outside the LRN laboratories with laboratories that have validated LDTs and use those as reference tests instead.

**Kristian Roth:** Sure. Thanks for that question. Maybe I'll start, and then Noel, if you've got additional information, please add that. So I think the validation pathway for test developers for monkeypox does include contrived samples. So these are samples, which would be spiked in at a series of concentrations tested, and then you would be comparing the outcome of your test with the known result of those samples.

So there is the opportunity to validate with those types of samples, which, of course, would not need a comparative method or clinical study. So that may relieve some burden on developers to get tests to market and certainly would help, since you don't have to have a comparative method. And the other option-- hopefully it's been mentioned previously-- is that there are commercial labs which are running that CDC test. And any of those commercial labs could be contacted as another source of information for your clinical study.

**Leslie North:** OK. Thank you.

**Joseph Tartal:** OK. Thank you, Leslie. Our next question is from Devy. I'm unmuting your line. Please unmute yourself and ask your question.

**Devy Emperador:** Hi, I'm Devy Emperador from [INAUDIBLE]. My question is on whether FDA will be also reviewing antigen-based tests.

**Kristian Roth:** Yes, thank you for that. We will certainly be reviewing antigen-based tests. We plan to release a template for these types of tests in the coming weeks. We have noted that it is a priority review category for us. So once we start receiving tests and once folks are more generally aware of our validation recommendations, we expect to engage with a number of parties on looking at antigen tests.

It's perhaps helpful for companies to reach out to the Independent Test Assessment Program. This is the ITAP program that's run through NIH. They are currently looking for folks that are developing antigen tests to partner with for the ongoing ITAP activities that are kind of an extension from the COVID ITAP activities. So that's another avenue for you as well.

**Devy Emperador:** Many thanks.

**Joseph Tartal:** Thank you for your question. Wenli is the only question I'm seeing remaining. I'm unmuting your line. Please unmute yourself, Wenli, and ask your question.

**Wenli:** Oh, thank you very much. So this is Wenli Jao from XYZ Laboratory. And I just want to further clarify the question about this single target in the multiplex or to target the more assay design question.

So I just want to understand a little more about the FDA's intention right now. So right now it's a monkeypox specific problem right now. So then in terms of the assay design, we can't always do a monkeypox specific assay. Regardless one target or two targets, they all target to monkeypox. Two target is better than one target because of the mutation concerns and that.

But if we look further in the future, if this assay should be used for the other orthopox, then it's better right now we just put the one target as the target for the other orthopox, rather than just to focus on the monkeypox. So therefore, we can put one for monkeypox, another one for another orthopox. So this is just a slightly different strategy. I would like to ask for your opinion in terms of this multiple target assay design.

**Kristian Roth:** Yeah, thanks. Hopefully, I was clear in the prepared answer. But I will-- of course, we will review single-target tests. There's nothing that prohibits you from sending a single-target test. That's a risk that you can take. So of course, with COVID, quite a bit of mutations-- it's a different virus, different

epidemiology. But still, I think we do want to safeguard test resilience with multiple targets. So I think having one monkeypox target and a non-variola orthopox target in the same test is a fine approach.

I think we would agree with that approach, and it certainly does fulfill that multiple target goal. So of course, it's up to you. But that seems like a good strategy to us.

**Wenli:** Alright. Thank you.

**Joseph Tartal:** Thank you. Our next question is from Annabel. Annabel, I'm unmuting your line. Please unmute yourself and ask your question.

**Annabel:** Hi, I know today's town hall is about monkeypox. I'm not sure if you're going to accept questions about COVID development and the updated policy. Would that be acceptable today?

**Kristian Roth:** Why don't you ask your question, and we'll see if we can get to it?

**Annabel:** Thank you. So we do understand with the new policy that EUA supplements will now be accepted only if they fulfill a condition of an existing EUA, and that otherwise we should be pursuing either direct De Novo or 510(k). So I was wondering whether that means that supplements for adding on a sub-brand or changing a box label would no longer be accepted. Is that a correct understanding?

**Kristian Roth:** It looks like we don't have too many monkeypox questions today, so I think we can get to this. I think, as many of our answers are, it really does depend. I think in general, we're likely not to look at that. If it is something that's critical to-- that businesses required or if there's some kind of other really pressing business need, that's something that you could ask us through the inbox-- the COVID-19 inbox-- and say, hey, here's what I plan to send in as a supplement. And we're glad to give you a priority determination on that.

**Annabel:** OK. Thank you very much.

**Joseph Tartal:** Thank you. Niya, I'm unmuting your line. Please unmute yourself and ask your question.

**Niya Su:** Hello, this is Niya Su from Coyote Bioscience. And thank you for taking my question. This is for monkeypox. So for high throughput test for CLIA high complexity use, I would like to confirm if the clinical evaluation with contrived samples for initial EUA submission can be conducted in an internal testing site.

**Kristian Roth:** Mm-hmm. Yes. I believe we don't require that testing to be done at a CLIA-certified lab. And certainly for this type of test, I think we don't object to you running that evaluation at your particular site-- single site.

**Niya Su:** OK. So it's OK to conduct in an internal site rather than--

**Kristian Roth:** Yes.

**Niya Su:** Thank you.

**Joseph Tartal:** OK. Thank you for your question. So with that, that is our last question that we have today. Thank you, everyone, for participating today. And I want to again, thank our panelists, Kris and Noel, as well.

Today's virtual town hall presentation and transcript will be posted on the "Virtual Town Hall Series - Test Development and Validation During Public Health Emergencies (Monkeypox and COVID-19)" webpage under the section "Previous Town Halls for Test Development and Validation During Public Health Emergencies." For specific questions about monkeypox diagnostic development, you may send an email to MPXDx@fda.hhs.gov.

Please remember to join us for the next virtual town hall for monkeypox test developers, scheduled for Wednesday, October 12 from 12:05 to 1:00 PM Eastern time.

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

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