

CDRH Virtual Town Hall #97
Monkeypox Test Development and Validation
November 9, 2022

CDR Kim Piermatteo: Hello, and welcome, everyone, to today's Virtual Town Hall, number 97, for monkeypox test developers. Today, we will discuss and answer your questions about diagnostic tests in response to the monkeypox public health emergency.

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 and CDRH's Office of Communication and Education. And I'll be your moderator for today's Virtual Town Hall.

Our panelists for today are Toby Lowe, Associate Director for Regulatory Programs in 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 Toby is Dr. Kristian Roth, Deputy Director of the Division of Microbiology Devices, also 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. Then we'll answer your previously emailed monkeypox test development and validation 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 today via the Zoom app and not through a web browser to avoid any technical issues.

Our next scheduled Virtual Town Halls are on November 30 and December 14 for monkeypox and COVID-19 test developers. You may refer to our webpage titled "Virtual Town Hall Series - Test Development and Validation During Public Health Emergencies for COVID-19 and Monkeypox" webpage 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 for monkeypox and COVID-19 test developers, which was held on October 26, 2022, have been posted to CDRH Learn. I have provided a screenshot on this slide where you can find those materials in CDRH Learn.

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

Toby Lowe: Thanks, Kim, and thanks for everyone. Thanks to everyone for joining us again for the town hall. I've got a quick update, and then we'll get right into questions. So we just wanted to briefly discuss the monkeypox test policy guidance and the process for EUA requests as previously discussed on the town halls and in the monkeypox test policy guidance.

The FDA's decision to review and process an EUA request is based on considering the public health need in an emergency. So the guidance discussed the types of monkeypox tests that we intend to prioritize for review, including those for which FDA received and intent to submit by October 13th. And those were logged in as pre-EUA. We have responded to some of the pre-EUAs to let sponsors know whether or not we would be prioritizing review of their test. And we have begun review of some of those EUA requests accordingly.

If you have not yet received a response on your pre-EUA, please be aware that we are still considering some of them in the context of the shifting needs of the public health emergency. And we will get back to you with a response. We also want to note that for tests we do intend to prioritize, we will work with the sponsor during the pre-EUA or the EUA review to discuss any specifics pertaining to the submission, including study design and potential needs for post-authorization study.

There is general information on these topics in the template. And we do continue to respond to general questions on the town halls. And then the more specific issues will be discussed during the particular review. And with that, Kim, I can hand it back to you. We can get into the questions.

CDR Kim Piermatteo: Great. Thank you, Toby, for those remarks. We will now answer your previously emailed questions about monkeypox test development and validation. Please note, we do receive some emailed questions that are a little 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.

So Toby, I'll be directing these previously emailed questions to you. The first question is, due to the rapidly declining incidence of monkeypox cases, is it acceptable to perform clinical evaluations using frozen retrospective samples?

Toby Lowe: Thanks, Kim. As noted in the molecular diagnostic EUA templates, frozen samples may be used if there is provided analytical data that demonstrates that freezing does not affect the accuracy of test results compared to freshly collected samples. We do recommend performing a fresh versus frozen study to support the use of frozen retrospective samples. And you can refer to the template for recommendations on study design documenting your study protocol and the preferred format for providing your data in an EUA request.

CDR Kim Piermatteo: Thanks, Toby. Alright, our next previously submitted question has two parts. The first part is, due to the rapidly declining incidence of monkeypox cases, is it acceptable to use contrived samples for the clinical evaluation? The second part asks, do test developers need to notify the FDA before proceeding with a contrived clinical study?

Toby Lowe: Thanks, Kim. Again, the EUA templates do provide information regarding clinical study design recommendations for molecular diagnostic monkeypox tests. And there's also additional information on the FDA's FAQ on testing for monkeypox web page, including information on appropriate test materials for validation.

So as noted in the molecular diagnostic templates, at this time, the FDA's initial clinical validation recommendations for molecular tests using lesion swab samples include the use of contrived specimens. And test developers do not need to notify FDA prior to performing a contrived specimen clinical study.

It's important to note if natural clinical samples become more widely available. We may revise this recommendation. And if no natural clinical specimens are available at the time of your EUA request for a monkeypox virus molecular diagnostic test, we recommend that contrived specimens in the clinical validation study be prepared using individual unique natural clinical specimen matrices such as human

skin lesion material specimens spiked with quantified material to create the quantity contrived specimen.

CDR Kim Piermatteo: Thanks again, Toby. That wraps up the previously emailed questions. We will now move to take your live questions. To ask a live question, please remember to 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.

So our first live question is coming from Ashfaaq. Ashfaaq, I have unmuted your line. Please unmute yourself and ask your question.

Ashfaaq Ismail: Hi, Kim. Thank you very much for allowing me onto the town hall meeting. I appreciate it. I'm a regulatory and quality consultant based in the UK. My quick query was that my specialty comes from mainly from software as a medical device. And I was just wondering what level of, like, validation testing would be acceptable to allow emergency use authorization in the cases for software as a medical device that might be used for, say, monkeypox testing or COVID testing, et cetera?

I could appreciate it might be a bit, perhaps, a general wide-ranging query. But I was just-- I was just interested to move with regards to what level of, like, validation testing or test coverage that the FDA would accept under emergency use authorization.

Toby Lowe: Yeah, thanks for that question. Some of that may depend on what the software is intended to do. Kris, do you want to weigh in on that?

Kristian Roth: Yeah, exactly. I think the validation-- I think there's two elements of the validation. One would just be the functions of the software, right? So that would be your regular validation that you would do for any software. And then you're going to also have a performance evaluation as well. And that's really what's going to be driven by your intended use.

So we did just release the final version of the Clinical Decision Support Software guidance. That, of course, applies to more traditional regulatory pathways. But it does give you some insight into software as a medical device and what we consider a medical device and not. Are you maybe asking about level of concern as well?

Ashfaaq Ismail: Yeah.

Kristian Roth: Yeah, so I think you'd have to go through the software validation guidance document. Just, there's a flowchart in there that would help you evaluate the level of concern.

Ashfaaq Ismail: Yes.

Kristian Roth: It's probably going to be moderate. I mean, most IVD softwares are moderate. However, again, you're really going to have to take your intended use and take it through that kind of decision-making flowchart that's in the software validation guidance.

Ashfaaq Ismail: OK. Would it be possible to provide link at some point to the guidance just to make sure I've got the latest version handy? That'd be great if possible.

Kristian Roth: Sure. And it may not be the easiest to provide the link here. But if you send an email to the MPXDx email address, we can certainly provide those links to you.

Ashfaaq Ismail: That'd be great. Thank you very much for that.

Kristian Roth: Great. Thank you.

CDR Kim Piermatteo: Thanks for that question, and thank you, Toby, and Kris, for that response. Alright, our next question is coming from Art. Art, I have unmuted your line. Please unmute yourself and ask your question.

Art, are you able to unmute your line?

Art, we are unable to hear you if you are speaking. Are you unmuted still? OK. Art, I'm going to go ahead and give you one more chance. I'm going to give you permission to talk.

OK. Art, if you're speaking, we can't hear you. So I'm going to go ahead and move on. At this time, I don't see any more raised hands. So I would like to make a call out. If you have a question for our panelists today, please raise your hand.

Alright, next caller, I'm calling on Vicky. Vicky, I have unmuted your line. Please unmute yourself and ask your question.

Vicky Huang: Hello, this is Vicky. Can you hear me?

CDR Kim Piermatteo: Yes, we can.

Vicky Huang: OK, yeah. I'm together with my colleague, Art. And he tried to unmute himself, but it is veiled. But I'm going to ask here.

Art Berrun: For some reason, this computer's working. OK, so we have to use the contrived samples. And my question is, if we go-- we're getting these samples from a lab that's a LDT. So that's not a validated assay to run. Is it feasible to use one of the five clinical or five commercial labs to get validated for clinical validation, so a positive. So say, for example, like Sonic Healthcare would validate our samples. Would it then be feasible to take those samples and use them for our contrived clinical test or evaluation?

Noel Gerald: OK.

Toby Lowe: You want to—

Noel Gerald: Yeah, I can take a first stab at that. So if I'm understanding you correctly, so your question is about samples-- real samples that you have-- clinical samples that you've sourced from some other place and whether you can send them to one of the five commercial labs that are running the cleared CDC test for evaluation. Is that's your question?

Art Berrun: Yeah, so the idea is that we would take them to there to get validated via this assay and then use that data to facilitate or contrived clinical specimen study.

Noel Gerald: Contrived. OK, so there's two different things. One, I'm not certain that the five commercial labs would be accepting samples for that reason. I suppose that you could always ask. But I think—

Art Berrun: Yeah, we did get validation from that they would run that here.

Noel Gerald: Right, yeah. But I think that the other part of this is that when we are talking about contrived specimens, they were recommending that you have it be quantitated. You want to have-- yeah, the material that you're spiking that you have some sort of quantitation for that. And that's not something that the cleared assay is cleared for currently. So you would still need to have some way to demonstrate how you quantitated the material that you're spiking.

Art Berrun: OK, so what would be the recommendation for that?

Noel Gerald: Yeah, so, I mean, our FAQ page has a list of material that you could use, which is not native clinical sample derived if you would want to take that route. But really, for those things, it's a separate question. If you were just testing real clinical samples not contrived, then you would need an appropriate comparator from a lab that's authorized to run that test.

But when you're just talking about contrived, the question isn't really confirmation with the cleared assay. It's how it's quantitated and whether that's acceptable. That makes some sense.

Vicky Huang: OK, this is Vicky. And I want to keep asking. Yeah, it looks like there's two way for us. One is prepare the contrived samples. And another is we can get to some clinical samples from a LDT lab who already notified the FDA and list it on the website of the FDA. Those clinical samples under PHI. So we cannot get any patient information, but they are real patient samples.

We plan to use those samples to do a validation. So we could do-- can we do that validation using those samples? Parts we give to, for example, the five labs of the CDC certified to validate the CT value. And a part of those samples, we use for our own lab or maybe our-- in the clinical-- in the CLIA lab to do the validation for us to compare-- to compare those CT values.

Noel Gerald: I see. It's a little bit more complicated of a question. So now, we're talking about use of real clinical samples, not contrived.

Vicky Huang: Yes.

Noel Gerald: And I think that when you're in that category, the general recommendations that are in the template would still apply, regardless of whether the lab that you're initially sourcing them from was notified or not. In order for them to be used in your performance calculations, we would need there to be an appropriate comparator. Something as recommended in the template, which at this time, is the cleared CDC assay.

In terms of-- I don't think that we've really entertained much beyond that. It seems like you're asking about some sort of comparison study to find what the results would be with the cleared CDC test. But really, if you had the cleared CDC test results with CT values for each of those samples, that would be all that is needed. So whatever previous results from an LDT, wherever it came from, wouldn't really be taken into consideration for the performance. But it is still challenging as we've mentioned on previous townhalls.

You sometimes get the cleared CDC results for example, this does not already natively have it. And in those cases, it seems that the most straightforward way would be to if you can get access to samples that already have the cleared CDC test results.

Vicky Huang: OK, OK, thank you.

Noel Gerald: Sure.

CDR Kim Piermatteo: Thank you, Vicky, and Art, for that question. And thank you, Noel, for that response.

At this time, I do not see any more raised hands. I will make one last call out. If you have a question, please raise your hand at this time.

OK, seeing none. Then I am going to go ahead and move to close, to close today's virtual town hall. Today's Virtual Town Hall and presentation and transcripts will be posted to CDRH Learn under the section titled "In Vitro Diagnostics" and the subsection titled "Virtual Town Hall Series." If you do have additional questions about monkeypox diagnostic development, please feel free to send an email to MPXDx@fda.hhs.gov.

And lastly, our next-- as a reminder, our next Virtual Town Hall will be for monkeypox and COVID-19 test developers on Wednesday, November 30th, 2022 from 12:05 to 1:00 PM Eastern Time.

This concludes today's Virtual Town Hall. Have a wonderful day.

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