Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program
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Moderator: CDR Kim Piermatteo

CDR Kim Piermatteo: Hello and welcome everyone to today's CDRH webinar. Thanks for joining us. This is Commander Kim Piermatteo of the United States Public Health Service, and I serve as the Education Program Administrator in the Division of Industry and Consumer Education in CDRH's Office of Communication and Education. I'll be the moderator for today's webinar.

Our topic today is the final guidance titled "Oncology Drug Products Used with Certain In Vitro Diagnostic Tests, Pilot Program," which was issued on June 21, 2023. This guidance is intended to pilot a new approach to provide greater transparency regarding performance characteristics that certain tests for oncology biomarkers used with certain oncology drug products should meet.

During today's webinar, we will explain the scope and goals of the new voluntary pilot program for certain oncology drugs used with certain in vitro diagnostic tests. We will describe how to complete the CDRH templates for collecting and providing performance characteristics and validation information for clinical trial assays under the pilot program. And answer your questions about this program.

Before we begin, I'd like to provide a few reminders for the webinar. First, please make sure you've joined us through the Zoom app and not through a web browser to avoid technical issues. Second, the intended audience for this webinar is industry. Trade press reporters are encouraged to consult with the CDRH Trade Press Team at CDRHTradePress@fda.hhs.gov. And members of national media may consult with the FDA's Office of Media Affairs at FDAOMA@fda.hhs.gov. And lastly, we look forward to interacting with you during the live question-and-answer segment of today's webinar. If you have a question, please wait, and raise your hand at the end of today's presentation to get into the queue.

I now have the pleasure of introducing our presenters for today's webinar, Dr. Timothy Stenzel, Office Director of the Office of Health Technology Number 7, or OHT 7, for In Vitro Diagnostics within the Office of Product Evaluation and Quality, or OPEQ, in CDRH, and McKenna Tennant, Policy Analyst in OHT 7 and OPEQ as well.

We'll begin with opening remarks from Dr. Stenzel, then a presentation from McKenna, and then field your questions about our topic. Thank you all again for joining us. I'll now turn it over to Tim to start today's presentation.

Timothy Stenzel: Hi. I am Tim Stenzel, Director of the Office of In Vitro Diagnostics. Thank you all for being here today. We are excited to have the opportunity to host this webinar to walk through FDA's new voluntary pilot program for certain CDER-regulated oncology drug products used with certain in vitro diagnostic tests. Given the public health importance of such in vitro diagnostic tests for determining a patient's cancer treatment, the guidance was implemented immediately.

We will first start by providing an overview of the scope and goals of the pilot program and then turn to walking through our recommendations for how to complete the pilot program's templates for collecting and providing performance characteristics and validation information for clinical trial assays, when requested by the FDA.

We thank you for joining today's webinar and look forward to the live Q&A at the end of the presentation. McKenna Tennant will now continue with the slide presentation. McKenna?

McKenna Tennant: Thank you, Tim. As mentioned, this webinar will focus on the final guidance for immediate implementation, "Oncology Drug Products Used with Certain In Vitro Diagnostic Tests, Pilot Program," issued earlier this year.

Thank you all for joining today's webinar on the oncology diagnostics pilot and associated clinical trial assay, or CTA templates. There are two key learning objectives for today. The first is to identify the scope and goals of the new voluntary pilot program for certain oncology drugs used with certain in vitro diagnostic tests. And the second is to be able to describe how to complete CDRH's templates for collecting and providing performance characteristics and validation information for CTAs under the pilot program, when requested by FDA.

I will start today's talk with a very brief overview of some of the key features and highlights of FDA's companion diagnostics policy and program for relevant background, talk about one of the challenges we face within the current companion diagnostics program, and then talk about the scope and goals of the new voluntary pilot program that is aimed at helping address that challenge.

As some of you may know, FDA defines a companion diagnostic as an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. Companion diagnostics can have different uses. They can be for identifying patients who are most likely to benefit from the therapeutic product, identifying patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product, identifying patients in the population for whom the product has been adequately studied and found to be safe and effective, or, in other words, for treatment selection when there is insufficient information about the safety and effectiveness of the therapeutic product in any other population, or monitoring response to treatment with a therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.

As described in FDA's final guidance document from 2014, "In Vitro Companion Diagnostic Devices," some key features of FDA's companion diagnostic policy that are most relevant to today's presentation include that ideally, a therapeutic product and its corresponding companion diagnostic should be developed and authorized at the same time, and the use of a companion diagnostic with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product.

The current companion diagnostics program continues to help assure that patients have access to safe, effective, and high-quality FDA-authorized companion diagnostic devices. One challenge that arises in the current environment, however, is the use of laboratory developed tests, or LDTs, in circumstances where there is not an FDA-authorized companion diagnostic.

As described in FDA's companion diagnostic guidance, there are specific circumstances where FDA may decide to approve a therapeutic without authorizing a corresponding companion diagnostic at the same time. And as stated in the companion diagnostic guidance, this happens when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment

exists and the benefits from use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an FDA-authorized companion diagnostic.

In use cases, tests offered as LDTs with unknown performance are being used for patient treatment decisions. For the purposes of FDA's guidance, "Oncology Drug Products Used with Certain In Vitro Diagnostic Tests, Pilot Program," the term LDT means a type of in vitro diagnostic device that is designed, manufactured, and used within a single-site CLIA-certified laboratory that meets the requirements for high-complexity testing. Historically, FDA generally has exercised enforcement discretion with respect to most LDTs such that, except in certain circumstances, FDA generally has not enforced applicable requirements with respect to most LDTs.

For tests that provide information that is essential for the safe and effective use of a therapeutic product, in circumstances where FDA decides to approve a therapeutic without authorizing a corresponding companion diagnostic at the same time, LDTs are being used. And while in these cases, the benefits from use of the therapeutic product were considered to outweigh the risks from the lack of an FDA-authorized companion diagnostic, that doesn't mean there are no risks. There are risks, including the use of LDTs that might not work as intended.

While LDTs play an important role in our health care system, the FDA has become increasingly concerned that LDTs currently used in the US might not provide patients with accurate and reliable results. For example, recent publications have documented LDTs that are inaccurate, including those used to identify patients for treatment with specific drugs. Use of inaccurate test results can negatively impact treatment decisions. One step that may be helpful in reducing the risk of using LDTs is to recommend and make transparent minimum performance characteristics for tests used to identify patients for drug treatment.

That's why, in June of this year, FDA issued a final guidance to announce and describe a new voluntary pilot program for certain oncology drug products used with certain corresponding in vitro diagnostic tests. The guidance titled "Oncology Drug Products Used with Certain In Vitro Diagnostic Tests, Pilot Program" can be found on FDA's website. As described in the guidance, FDA is piloting a new approach to provide transparency regarding minimum performance characteristics that certain tests should meet if they are to be used to select treatment with certain oncology drug products. As I mentioned on the previous slide, we believe this is one step that may be helpful in reducing the risk of using LDTs for oncology drug treatment decisions when there is not an FDA-authorized companion diagnostic.

The pilot program does not alter the standards for approval of the oncology drug products reviewed under the pilot program or for marketing authorization of corresponding companion diagnostics. Since the majority of therapeutic products that require use of an in vitro diagnostic test for patient selection but are approved without contemporaneous approval of a companion diagnostic, are in the oncology space, piloting this approach for oncology drug products is a logical place to start. Further, since the majority of FDA-cleared and approved companion diagnostics are for oncology drug products, we have the most experience with in vitro diagnostic tests used in the selection of such treatments and are therefore most comfortable piloting such an approach in this space.

Before we dive into the details of the pilot program, it's important to understand the scope of the program, which is limited to certain scenarios. Specifically, the pilot program is limited to nine drug sponsors and CDER-regulated oncology drug products for which FDA determines use of in vitro

diagnostic test is needed to identify the intended patient population. No satisfactory alternative treatment exists, and the anticipated benefits from the use of the drug product are so pronounced as to outweigh the anticipated risks from approval of the drug product without an FDA-authorized companion diagnostic.

The corresponding clinical trial assays are limited to CDRH-regulated tests for which there is a well-validated reference method, well-validated comparator method, and/or well-characterized materials that can be used to support test accuracy and that use the same technology as a previously FDA-authorized companion diagnostic for any indication.

Although the initial phase is for nine drug sponsors, if appropriate based on the experience during the initial phase, FDA anticipates it may expand the pilot to evaluate additional sponsors for acceptance.

Now let's talk a little bit about the pilot program at a high level. As is the case for FDA-authorized companion diagnostics, under the pilot program, if the FDA concludes that the drug product meets the applicable standards for its approval, FDA intends to rely on the same pivotal clinical trials that support approval of the drug product to establish the clinical validity for the clinical trial assays used in those trials. Given the limited type of tests eligible for use in the pilot program, as described on the prior slide, FDA believes that in general, the clinical validity of these CTAs can be extrapolated to additional tests of the same type with similar analytical performance when established through properly conducted validation studies.

Under this pilot program, the FDA will be making transparent on its website recommended minimum analytical performance characteristics that would support extrapolating the clinical validity established in the drug trials to additional tests of the same type. FDA anticipates that the approved drug labeling will specify that the drug is indicated for patients identified as exhibiting a named biomarker by in vitro diagnostic tests that have FDA's recommended performance characteristics.

CDRH intends to provide on its website the recommended minimum performance characteristics for these tests. FDA also anticipates that both the approved drug labeling and CDRH's website will specify relevant test characteristics for the in vitro diagnostic tests for use with the drug, such as the biomarker detected and test method, including the specimen type.

So how does this happen logistically? In circumstances where the FDA approves a drug without approval of a companion diagnostic at the same time, the FDA will request the drug sponsor provide performance information for the tests used to enroll patients into the clinical trials that support drug approval. Based on an assessment of that information, the FDA will post to the FDA website the minimum performance characteristics recommended for similar tests that may be used to select patients for treatment with the approved drug.

Providing transparency of minimum recommended performance characteristics aims to help facilitate better and more consistent performance of these tests, resulting in better drug selection and improved care for patients with cancer.

To be considered for the voluntary pilot program drug sponsors should submit a statement of interest to their investigational new drug application, new drug application, or biologic license application. Upon receipt of the statement of interest, FDA will follow up with no more than nine sponsors to request

specific information to enable FDA to make a decision concerning acceptance into the pilot, based on certain factors described in the guidance. One of those is the oncology drug sponsor being able to collect and provide the analytical validation data and performance characteristics, as recommended in FDA's templates, for all CTAs used for the enrollment of the pivotal clinical trial.

On its website, the FDA has provided a series of templates that oncology drug product sponsors, when requested by the FDA, can use to facilitate the provision of performance characteristic information on the CTAs used in their clinical trials. These templates describe the performance characteristic information that should be provided by the oncology drug product sponsors when requested by the FDA, which drug sponsors would need to obtain from the test developers.

The templates available on the website are based on test technology. And currently on our website, there is a next-generation sequencing test template, a PCR test template, a Sanger sequencing test template, an immunohistochemistry test template, and a fluorescence in-situ hybridization test template. We will turn to more details on these templates during the second half of this presentation.

Drug development programs from drug product sponsors accepted into the pilot program will fall into one of two buckets, the oncology drug pivotal trials are not started at the time the guidance was issued on June 2023, or the oncology drug pivotal trials were initiated prior to June 20, 2023. We sometimes call this the prospective approach and retrospective approach. Procedures for the pilot and accepted sponsors vary based on whether the programs are prospective or retrospective. For pivotal trials that have not started as of June 20th of this year, FDA will provide minimum validation and performance characteristics for CTAs to enroll the drug product's pivotal clinical trial prior to the start of the trial. FDA expects the CTAs for trial enrollment will meet or exceed these validation and performance characteristics. And if the drug is ultimately approved, FDA will recommend minimum performance characteristics for IVDs to be used with that drug based on performance of the CTAs used in the clinical trials.

For trials that were initiated prior to June 20th of this year, FDA will work with the drug sponsors accepted into the pilot to review the performance characteristics and validation information for each CTA and, provided the data are sufficient, recommend the minimum performance characteristics within the NDA or BLA application review time frame.

In summary, the key takeaways for the pilot program described today are that FDA believes transparency regarding minimum recommended performance characteristics will help facilitate development of better and more consistently performing tests, resulting in better drug selection and improved care for patients with cancer. However, this pilot program will not assure that LDTs available to patients are safe and effective. Separately, FDA issued a notice of proposed rulemaking, proposing a policy under which FDA intends to phase out its general enforcement discretion approach for LDTs.

Now we will move on to learning objective two and focus on the pilot program templates for collecting and providing performance characteristics and validation information for CTAs under the pilot program.

As previously touched on, the pilot templates on CDRH's his website are intended for use by oncology drug product sponsors who have submitted the statement of interest for the pilot program. We encourage oncology drug sponsors interested in participating in the pilot to submit a statement of interest to their IND, NDA, or BLA.

These templates should only be used to provide information that should be submitted to FDA, only when requested by FDA. The templates are to help oncology drug sponsors to collect and provide validation information and performance characteristics for each CTA used in the pivotal clinical trials for drug products under the pilot program.

The information recommended in the templates is largely technology specific, so, it varies by template. However, there are four general sections in each of the CTA templates, general laboratory information, general test information, validation studies, and data tables.

Five templates are available on CDRH's website for download as Word documents, with various free text and yes-or-no selection box options for filling out requested information. We aim to make these templates as user friendly as possible to simplify the process. And for today's webinar, we will walk through elements of the Next-Generation Sequencing, or NGS TTA template. Please note that FDA's collection of the validation and performance characteristic information for CTAs used under the pilot does not mean we are authorizing or deeming acceptable the performance of these assays.

So, the template first asks for general laboratory and test information. In the general laboratory information section, you should fill out information about the laboratory performing the CTA, relevant contact information for that laboratory, and the test name. As shown on this slide, the template includes a question that asks whether the CTA is commercially available. If yes, you would provide the kit and manufacturer name as well as describe any modifications that may have been made to the kit, for example, to specimen type. If the CTA is not commercially available as described in the template, you should provide the analyte or analytes detected, such as single-nucleotide variants for T790M and the EGFR gene in DNA. And describe the test method, including the specimen type, for example, hybrid-based capture from formalin-fixed paraffin-embedded, or FFPE breast tumor tissue.

As described in the template, regardless of whether the test is commercially available, we recommend you provide the following information, CTA components: such as probes, reaction mixes, and enzymes; extraction methods; instrument or platform used; minimum tumor content and nucleic acid amount and range; description of the positive and negative control, their respective use, and what they respectively measure; and a summary of the bioinformatic workflow used for the test, including the sequence alignment, germline filter, and variant calling processes.

The general test information section recommends providing your determination of calling rules, acceptable sequencing quality metrics, and clinical cutoff. For calling rules, please provide the prespecified variant classification rules used to identify the presence or absence of the analytes that the CTA is intended to detect. As described in the template, we recommend you provide your sequencing quality metrics for run acceptability at the sample, variant, and flow cell level using a table, as exemplified by table one. These include coverage uniformity, based quality score, mapped reads, strand bias, variant allele frequency, minimum number of mutant reads, percent pass quality filter, percent greater than Q30, and any other metrics you may have implemented for run acceptability. We also recommend you briefly summarize the prespecified clinical cutoff that was used to enroll subjects in the clinical trial.

We are now moving on to the validation studies section of the template. While we are not going to go through all of these subsections today in detail, at a high level, the validation study section of the NGS

template requests information on samples used in the validation studies, for example, a summary on how surrogate samples were constructed if used, information on the source of reference samples or materials if used, and the number of different types of samples used in each validation study. Information is also requested on comparator or orthogonal methods, analytical accuracy of the CTA, limit of detection determined, precision studies, interfering substances studies, inclusivity, cross-reactivity studies, stability studies, and NGS liquid biopsy specific information.

I'm first going to discuss requested information on comparator and orthogonal methods and analytical accuracy of the CTA. Comparator or orthogonal methods are used to characterize samples and/or validate the CTAs. For this section of the template, please provide information on any comparator and orthogonal methods used to characterize samples and validate the CTA. And the studies they were used for in table three, for example, analytical accuracy, limit of detection, precision, and interfering substances for orthogonal or comparator methods used for sample selection and characterization, and analytical accuracy when used for validation. If LDTs were used as comparators, we recommend you provide the laboratory's name and address, as well as the stated accuracy of the comparator methods.

Now turning to the analytical accuracy concordance piece of the validation studies section of the template and what is recommended. Analytical accuracy of the CTA is determined relative to a reference method or validated comparator method or orthogonal method. For NGS-based tests, accuracy represents the degree of concordance or agreement of results between a sequence obtained from the test and the same sequence determined by the valid comparator method, or between a reference sample run on an NGS-based test and the high confidence sequence of the reference. If a comparator method is used, it should have similar panel content and sensitivity to that expected from the CTA, based on the test method and previous analytical testing. Well-characterized samples should be tested with both the CTA and comparator method.

So, for this section of the template please provide a brief summary of the study design, including the statistical data analysis methods used to determine analytical concordance. Details on the samples tested to demonstrate accuracy, of which the requested information varies by variant type, so variant allele frequency for SNVs and indels, chimeric reads for rearrangements and fusions, and copy numbers for CNVs. Please also provide, if the analytes are not individually validated, details on the samples tested to demonstrate panel-wide accuracy for representative panel variants, including variant allele frequency for SNVs and indels, chimeric reads for rearrangements and fusions, and copy number for CNVs, as well as a summary of analytical concordance between the NGS CTA and comparator for variants and genes evaluated for patient enrollment.

We will now look at the recommended concordance summary data on the next slide.

For analytical accuracy, we recommend you calculate positive percent agreement, or PPA, and negative percent agreement, NPA, between the CTA and the comparator method for representative variants in genes and for panel-wide accuracy as applicable. And provide concordant summary data in table 4, as you see here. The top part of the table is where you would input information on specific variants that have been individually validated. For example, SNV EGFR T790M. The bottom part of the table is where you would input information on panel-wide accuracy as applicable.

PPA is the ability of the test to correctly identify variants that are present in a sample and reflects the frequency of false negatives. NPA is generally defined as the proportion of correct calls by the assay for

the absence of a genetic variant. More specifically, for genetic tests, NPA is the probability that the assay will not detect a sequence variation when none are present. At this time, the table does not include calculations for PPA and NPA. As described in the template, we recommend you provide your calculated PPA and NPA in table four.

We're now going to look at the requested precision information in the validation studies section of the template.

Precision studies are performed to evaluate sources of variation in the test procedure to determine the repeatability and reproducibility of the test. Reproducibility for NGS-based tests involves measuring test variability under a variety of specified conditions, such as when using different operators, different operating conditions, different days of measurement, different instruments, et cetera, using the same sample, including samples around the test cutoff, and accounting for major sources of variability in the test.

Repeatability involves measuring test result variability when using the same operators, the same measuring system, the same operating conditions, and the same location, and replicating measurements on the same or similar objects over a short period of time.

For the precision section of the template, please provide a brief study design; the number of runs, days, instruments, reagent lots, operators, and replicates tested per sample; whether precision was evaluated at multiple sites, and if details are not provided for each analyte, details on samples tested to demonstrate panel-wide precision; if the study was not conducted with the end-to-end workflow, information on the part of workflow included and rationale; a summary of statistical data analysis methods to determine CTA precision; and a summary of PPA and NPA for variants and genes used for patient enrollment, and panel-wide precision, if applicable. Now, looking at the table to provide this information on the next slide.

We recommend using table six in the template to provide summary variant PPA and NPA information for precision. The top part of the table is where you would input information on specific variants that have been individually validated-- for example, EGFR T790M. The bottom part of the table is where you would input information on panel-wide accuracy as applicable.

We will now go through requested information on limit of detection, interfering substances, and inclusivity cross-reactivity studies.

Limit of detection, or LOD, is the lowest amount of genomic target that the test can consistently detect with a stated probability. LOD can be stated as the lowest variant allele frequency the test can detect for short variants, such as SNVs and indels, the lowest number of chimeric reads that the test can detect for gene fusions and large rearrangements, and the lowest copy numbers that the test can detect for chromosome amplifications, and the lowest number of rearrangements and CNVs the test can detect for structural variants.

LOD may also be based on tumor content. As described in the template, for the LOD section, please provide a brief summary of the study design, including the statistical data analysis methods used to determine LOD, a list of how many reagent lots were used in the LOD establishment and confirmation

study, and a summary of your precision study results. We recommend using table five of the template for the summary of your LOD study results.

Moving on to the interfering substances piece of the validation study section of the template, interfering substances studies evaluate the effects of potentially interfering endogenous and exogenous substances on test performance, for example, hemoglobin. As described in the template, for the interfering substances section, we recommend providing a brief study design summary, including statistical data analysis methods used to evaluate interference and a summary of results for each interfering substance tested in table seven. As shown here and in the template, table seven includes the LOD levels used, the number of samples, replicates per sample, failure rate, detection rate, and call rate.

Looking at the inclusivity/cross-reactivity section. Inclusivity/cross-reactivity studies evaluate the specificity of the primers or probes used to target specific genes or genomic regions. Specifically, these studies assess the potential for cross-reactivity of known cross-reactive alleles and homologous regions, such as pseudogenes, based on the targets interrogated by the test. We recommend you provide a brief description of the inclusivity/cross-reactivity study performed and a summary of the in silico cross-reactivity with nontargeted regions. While not on this slide, as described in the template, we also recommend that stability studies be conducted to support storage conditions, including the duration of storage for specimens, and stored intermediate products, as applicable. In the template, we recommend providing the stability for primary specimens, including the conditions and durations, and the stability for intermediate specimen products, such as library prep.

There is specific information requested in the templates for if the CTA uses liquid biopsy.

If this is applicable to your CTAs, in the NGS liquid biopsy specific information in the template, please describe any quality measures for the circulating tumor DNA samples, such as fragment analysis. Please document whether germline or clonal hematopoiesis of indeterminate potential, or chip variants, were excluded. Please describe the study to establish the CTA's Limit of Blank, or LoB, if LoB was performed for your CTA. LoB is determined as the highest measurement result that is likely to be observed with a stated probability for a blank sample, for example, analyte negative. And then, lastly, please describe how interference for the blood-based tests were assessed. For blood-based tests, short draws and unique components derived from the blood collection process could contribute to interference.

If you have any questions when using the template, please feel free to reach out to the CDRH mailbox in the guidance, OncologyPilotCDRH@fda.hhs.gov. Also, if you wish to comment on the guidance or the templates, we encourage you to submit a comment to the pilot program guidance document.

We hope that you found this template demonstration helpful. And to summarize, our goal is to make the collection and provision of test validation and performance characteristic information as easy as possible. The pilot CTA templates provided on our website, for which we walked through one of five available templates today, are intended to facilitate the provision when requested by FDA of analytical validation and performance characteristic information for CTAs used in pivotal trials for drug products under the pilot. This pilot program is one step that may be helpful in reducing the risk of using unauthorized LDTs for oncology drug treatment decisions.

CDR Kim Piermatteo: Thanks for that presentation, McKenna. Now we will transition to our interactive question-and-answer segment for today's webinar.

Before we begin, I'd like to go over how we'll manage this segment and a few reminders. To ask a question, please select the Raise Hand icon, which should appear on the bottom of your Zoom screen. I'll announce your name and give you permission to talk. When prompted, please select the blue button to unmute your line and then ask your question. When asking your question, please remember to limit yourself to asking one question only and try to keep it as short as possible. We appreciate that you may have a very specific question involving your device or scenario; however, we might not be able to answer such specific questions today. Therefore, we'll try to frame a broader response based on what's described in the final guidance and the pilot. After you ask your question, please lower your hand. And if you have another question, please feel free to raise your hand again to get back into the queue, and I'll call on you as time permits.

So, at this time, please go into Zoom, and you can select the Raise Hand icon to ask Tim and McKenna a question related to this pilot program.

Our first question is coming from Dun. Dun, I have unmuted your line. Please unmute yourself and ask your question.

Dun Liang: Thank you. Can you hear me?

CDR Kim Piermatteo: Yes, we can.

Dun Lian: This is Dun from Loxo@Lily. So, I have just one question. Is it necessary to collect performance characteristics, and how should one fill that template for an FDA-approved test or device?

CDR Kim Piermatteo: Thank you, Dun, for that question. I'm going to turn it over to McKenna to provide you a response.

McKenna Tennant: Hi. Thank you, Dun. So, yes, as part of the pilot program, if requested by FDA, we will be requesting validation and performance characteristic information from the CTAs used for enrollment in the trial, as that information will be used by FDA, provided that it's appropriate, to develop the recommended minimum performance characteristics should the drug be approved under the pilot program. Does that answer your question?

Dun Liang: Yes. Some of those tests, in our preparation for the pilot, is that they are actually FDA-approved, right. So probably not with the indication for this particular investigational drug, but they are approved. So, my question is, can we, do we need to extract those information, and how can we do that? Are we looking at those approved SSED or decision summary? You know, I'm asking those LDTs-- that are being approved.

McKenna Tennant: Yeah. So, if FDA-authorized kits are used for enrollment of the pivotal clinical trial, and it's not used as the approved indication for use, then, yes, labs should submit, or the drug sponsor should submit performance data. So, again, it would be when requested by FDA, we would expect the analytical validation data and performance characteristics for all CTAs used for enrollment, including if it's a kit. One thing to note is that the drug sponsor will need a right of reference from the owner or owners of the CTA data, such as the kit manufacturer.

Dun Liang: Thank you.

Timothy Stenzel: And I would also add, this is Tim, that if you make any modifications to the kit, a new sample type, maybe a new extraction method, we would want to see validation around that you do just normally.

Dun Liang: Thank you.

CDR Kim Piermatteo: Thank you Dun for your question. And thank you, McKenna, and Tim, for providing a response. Our next question is coming from Lynne. Lynne, I have unmuted your line. Please unmute yourself and ask your question.

Lynne: Hi there. Can you hear me?

CDR Kim Piermatteo: Yes, we can.

Lynne: Sure. I wanted to know if this pilot program and any of the LDTs that are put through this program, once the drug is approved, or prior to the drug approval, does this pilot program remove the need for the drug manufacturer to bring forth an approved CDx?

McKenna Tennant: Thank you for that question, Lynn. So, for drugs approved under the pilot program, FDA will determine the need for a post marketing commitment for the development of a companion diagnostic on a case-by-case basis. But I want to emphasize, in general, we would not expect a companion diagnostic or a post marketing commitment for the development of a companion diagnostic for drugs approved under the pilot program where FDA would be able and would be recommending and posting on its website minimum performance characteristics for the in vitro diagnostic test used to identify patients. So generally, we would not expect a PMC if we are able and will be recommending NPCs under the pilot program for that drug.

Lynne: OK, thank you.

Timothy Stenzel: And this is Tim. I would add that any drug sponsor that wants to discuss this in a little bit more detail, just reach out at the email address posted on the presentation and we'd love to engage in a dialogue about it as needed. Thanks.

Lynne: Thank you.

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

Staci J Kearney: Yes, hi, thank you, Staci Kearney from Elevation Strategic Development. You may not be able to answer this question yet, but if finalized, how could the proposed rule, going into effect, affect the drug label when an LDT is used to support drug approval, but an FDA-approved CDx does not yet exist?

McKenna Tennant: Thank you for your question, Staci. As we stated, this webinar is only about the pilot program.

Staci J Kearney: OK. Thank you.

McKenna Tennant: Thank you.

CDR Kim Piermatteo: Thanks, Staci. Our next question is coming from Valerie. Valerie, I have unmuted your line. Please unmute yourself and ask your question.

Valerie M Bella: Hello. Can you hear me?

CDR Kim Piermatteo: Yes, we can.

Valerie M Bella: Hello. My name is Valerie, I'm from Johnson & Johnson. I have a question. If the clinical trial is enrolled based on a local test, but you centrally confirm your results using an FDA-authorized test, would the NPCs be based off of the local test data or the central test? Or would it be a combination of both?

Timothy Stenzel: Can I ask a follow-up question before we answer? And that is, what is the test of record for enrollment in the study?

Valerie M Bella: It is, enrollment will be based on the local test results.

Timothy Stenzel: OK. Thank you. McKenna, do you want to handle this one?

McKenna Tennant: Yep. If enrollment will be based on the local test results, then we would expect analytical validation performance characteristic data from those local test results, and we would be recommending NPCs based on the performance of those local test results used for enrollment.

Valerie M Bella: Thank you.

McKenna Tennant: Thank you.

CDR Kim Piermatteo: Thanks, McKenna. Thanks, Valerie. Our next question is coming from Jean. Jean, I have unmuted your line. Please unmute yourself and ask your question.

Jean Y Chen: Hi, thanks. Hi, this is Jean Y Chen from Loxo@Lily. I have a question about collecting the local laboratory test data. So, as you know, the laboratory frequently change their tests, and the performance may change as those tests are changed. So how can the performance data be accurately collected for a specific version of the test that's used in the trial?

Timothy Stenzel: That's a challenging question. Generally hoped that an enrollment assay would not change during a drug trial. If it's necessary to make a change, it would be great to have information about those changes and also provided with the collection of local assay information so that the FDA can assess the original and any subsequent changes in their potential impact on performance. McKenna, anything else to add about my response?

McKenna Tennant: Nope. I think that sounds good. We would just still expect the validation performance characteristic information for that modified version of the assay because the goal of the pilot is if the drug is approvable, we would set the minimum performance characteristics based on the actual performance of the tests used for enrollment.

Timothy Stenzel: Yeah, and I can imagine that some of those changes might be minor and not impactful of performance. But still, we'd like to be aware of them.

Jean Y Chen: Thank you. And just to follow up, sometimes the trials may take a very long time to complete. And over time, as the performance of the tests change, how does FDA expect the sponsor to capture that?

Timothy Stenzel: You know, this is, perhaps should be expected, given long trials. I think, you know, if you could send us an email at OncologyPilotCDRH@fda.hhs.gov asking this question, I think having an offline conversation about this, especially internally so that we can give you the best answer, is going to be best at this point.

Jean Y Chen: Thank you.

CDR Kim Piermatteo: Thanks, Jean, for your question, and thanks, Tim, and McKenna. Our next question is coming from Carly. Carly, I have unmuted your line. Please unmute yourself and ask your question.

Carly McWilliams: Hi. This is Carly McWilliams with Roche Diagnostics. Can you hear me, OK?

CDR Kim Piermatteo: Yes, we can.

Carly McWilliams: Thank you. I have understood from a meeting that this pilot could potentially lead to down-classifications of companion diagnostics. And I wanted to know if there was anything that you could say about that?

Timothy Stenzel: McKenna, you want to handle that?

McKenna Tennant: Yes. I am happy to. So, this pilot program may facilitate regulatory submissions to FDA because the minimum performance characteristics developed through the pilot could be leveraged to support Premarket Application, or PMA approval, but the NPCs could also be leveraged to support the development of special controls.

I do want to note the pilot doesn't alter the standards for marketing authorization of companion diagnostics. So, kit manufacturers will still be required to obtain FDA authorization, which is typically currently sought through the PMA pathway for companions, but this pilot might help open up the De Novo pathway and, subsequently, the 510(k) pathway, if the statutory criteria for the De Novo pathway are met. And we are aware that many labs are interested in using FDA-authorized kits when available. And also, the availability of the De Novo or 510(k) pathways may also incentivize voluntary submissions for LDTs.

Carly McWilliams: Thank you very much.

CDR Kim Piermatteo: Thanks Carly for your question. Our next question is coming from Aaron. Aaron, I have unmuted your line. Please unmute yourself and ask your question.

Aaron Schetter: Hi, this is Aaron Schetter from AstraZeneca. And I just had a question about the interactions and the timings for companies to get feedback on clinical trial assay. As we start planning studies [inaudible].

CDR Kim Piermatteo: Aaron, you're breaking up a little bit. Would you mind speaking…

Aaron Schetter: Oh.

CDR Kim Piermatteo: There you go.

Aaron Schetter: OK. Yeah, I want to ask a question about, what do you foresee the interactions and the timing of those interactions for us, for companies to get feedback on one of the clinical trial assays they've selected would be sufficient? And the idea would be we would need to proactively plan to use them in our studies and get answers kind of in real time to be able to take advantage of it.

McKenna Tennant: Thank you for your question. So, we can't speak to kind of the timeline of reviews of statements of interest and acceptance of participants into the pilot. I will say that for accepted drug sponsors with prospective programs or programs that have not yet begun enrollment, as stated in the guidance, you know we will work with that sponsor to provide written feedback regarding validation of performance characteristics for the CTAs used for enrollment prior to the trial initiation. We can't speak to specific timing you know right now, but we will definitely be working interactively with the sponsor. I hope that gets at the question. Thank you. And I see Tim is also.

Timothy Stenzel: Yeah. I just want to add that we want to turn this around quickly when we have inquiries about this. And we know that it's important to increase certainty and decrease uncertainty in your decisions and we want to make this as easy as possible for you to decide whether or not to participate.

Aaron Schetter: OK, thank you.

CDR Kim Piermatteo: Thank you, Aaron, for your question. Looks like I'm going to circle back to Jean. Jean, do you have another question? I've unmuted your line. Please ask your question.

Jean Y Chen: Hi, thank you. Yes, I have another question. So, will all the analytical performance data that is submitted by the sponsor be public, be publicly available on FDA's website, or will any of the details or any of the data or information that we collect be publicly available?

McKenna Tennant: Thank you for your question. So, on CDRH's website, we will not be providing specific information about specific tests or labs. So, on our website, we will just be providing the minimum performance characteristic recommendations by technology type and per approved drug under the pilot program. Thank you.

Jean Y Chen: Thank you.

CDR Kim Piermatteo: Thanks, McKenna. Thanks, Jean. Our next question is coming from Shannon. Shannon, I have unmuted your line. Please unmute yourself and ask your question.

Shannon Bennett: Thanks. It seems like the guidance is really driven by the drug companies. If there is a laboratory that would be interested in participating in a pilot, how might they get involved?

McKenna Tennant: Thank you for your question. So, the pilot program is specifically for oncology drug product sponsors. So, we're going to be accepting, you know the scope is just for accepting drug sponsors. So, I just want to flag that. However, you know, we do get the question, are labs or drug sponsors supposed to fill out the templates? This is up to the oncology drug product sponsor. But the oncology drug sponsor should submit that information. If you have comments or questions on the guidance with respect to input from the lab community, we suggest you reach out to the CDRH inbox on the slides, or also submit comments to the docket of the guidance.

Timothy Stenzel: And, Shannon, I would also add that, certainly, you can make your desire known to participate to drug sponsors. I would expect you know a lot.

Shannon Bennett: Thank you.

CDR Kim Piermatteo: Thank you for that question. Our next question is coming from Songbai Wang. I've unmuted your line. Please unmute yourself and ask your question.

Songbai Wang: Hi, this is Songbai. Thanks. Can you hear me?

CDR Kim Piermatteo: Yes, we can.

Songbai Wang: OK. So, can FDA clarify what's the timing for recommended minimum performance characteristics? Specifically, is it before the clinical trial in the pilot to start or after the trial start, after the trial finish and the drug is approved?

McKenna Tennant: Thank you. So, FDA intends to recommend the minimum performance characteristics within the time frame for review of the NDA or BLA application. And we expect to post the minimum performance characteristics on our website at the time of drug approval.

Songbai Wang: OK. Thanks. From your presentation, I believe I saw somewhere that you indicate that said you would recommend NPC for the CTA, is, but that's.

Timothy Stenzel: Yeah.

McKenna Tennant: Yes, I can, oh, go ahead, Tim.

Timothy Stenzel: No, no. You now know what he's asking. So, thanks.

McKenna Tennant: Thank you. So, you are correct. And this was in the slide presentation, the discussion between, about the process difference for retrospective and prospective programs. So, for trials that have not yet begun enrollment and for accepted drug sponsors, we will work with the sponsor to provide our feedback in the form of minimum validation and performance characteristics for CTAs to be

used for enrollment prior to the start of the trial. We would only be providing those recommendations to that accepted drug sponsor. And then we would expect that the CTAs used for enrollment would meet or exceed those recommendations. And at the conclusion of the trial, and if acceptable, the drug is deemed approvable, we would develop the minimum performance characteristics and publicly recommend those based on the actual performance of the CTAs.

Timothy Stenzel: And then, McKenna, if you could you know address the, what we call retrospective in the guidance and how that differs.

McKenna Tennant: Yes. So, we consider, to clarify the difference between retrospective and prospective programs, retrospective programs are those that have already begun enrollment. And actually, it's those that have begun enrollment at the date of the guidance publication, which is June 20th of this year. And then prospective programs are those that have not yet begun enrollment, where we would work with the sponsor to provide feedback regarding CTA validation prior to the trial enrolling.

Timothy Stenzel: So, if the trial has already begun enrolling, then we would want you to collect the information, the drug sponsor would collect the information about the CTA, clinical trial assay, test performance characteristics. But if we interact with you before you start the trial, then we'll work with you to set those expectations so that the labs that enroll know you know what the expectation is.

Songbai Want: OK, thanks. That's very helpful. If I understood correctly, you mean that your final NPC that's recommended, that you post as final, that's after community trial, after drug review, after everything that's reviewed, right? But during the discussion with the sponsor for the prospective trial, you would recommend, and the validation, analytical validation, and the minimum performance characteristics. But that can change, sort of you are, your recommendation with that specific sponsor. And that may change and different, or that may be different than what you eventually, after you see all those clinical trial data and, finally, you post on your website for the NPC.

Timothy Stenzel: Yeah, yeah. So, we'll need to move on to probably at least one more question. Yes, the final performance expectations will be set after the drug is reviewed. You could imagine that we might set minimums before the trial begins but, when we're actually looking at the assays in the study, that they're well above the minimums and so, the minimums may be different. It's too hard to predict at this point. Thank you.

Songbai Wang: OK, thanks.

Timothy Stenzel: Time for one more question, maybe?

CDR Kim Piermatteo: Yes. The next person we're calling on is Kaben. Kaben, I have unmuted your line. Please unmute yourself and ask your question.

Kaben Schwartz: Yes. Good afternoon and thank you for the discussion. I just wanted to ensure I'm capturing a couple of key takeaways from this.

So, if a sponsor is conducting a clinical trial with an investigational drug that enrolls patients using a validated biomarker, and the sponsor wishes to rely on a commercially available CDx that is FDA-

authorized, then the sponsor may need to provide clinical data that was described in this webinar, along with a right of reference from the manufacturer. Is that correct?

McKenna Tennant: So, if the trial is using, sorry, if the trial is using local tests from labs, and those local tests are kits from manufacturers, then the right of reference would need to extend to both the laboratory running the test as well as the kit manufacturer. Does that get at your question?

Kaben Schwartz: Yes, yes, it does.

McKenna Tennant: Yes. Thank you.

Timothy Stenzel: Do we have time for one more question?

CDR Kim Piermatteo: Sure. We do, Tim. Alright, our next question is coming from Yaji Xu. I have unmuted your line. Please unmute yourself and ask a question.

Yaji Xu: Yeah, hello. This is Yaji Xu from Johnson & Johnson. I have a question related to some previous questions. Just, for example, if the drug sponsor decides to use not-yet-approved commercialized assay for trial enrollment, does this case fall into the scope of the pilot program?

McKenna Tennant: Thank you for your question. So, regarding the scope of the pilot program, the CTA has to use a technology of the same type as a previously FDA-authorized companion diagnostic, regardless of indication. And then there also has to be the availability of a well-characterized or well-validated reference method, comparator method, or other materials to support test accuracy. So that's the kind of scope of CTAs. With respect to can you use a kit or not, those are the only CTA scope limitations. And we would just expect that you be able to provide the validation and performance characteristic information from that kit if used as a CTA for your assay. So, again, just to reiterate, we expect the validation performance characteristic information for all the CTAs used for enrollment, which can include kits.

Yaji Xu: Thank you.

McKenna Tennant: Thank you.

CDR Kim Piermatteo: Thank you for that question, and thank you, McKenna, for your response. At this time, that wraps up our question-and-answer segment for today. Thank you all for your questions and for your engagement today. At this point, I'd like to turn it back over to McKenna to provide her final thoughts. McKenna?

McKenna Tennant: Thanks, Kim. So, yes, I want to thank you all again for joining, and we hope you found this pilot program overview and template demonstration helpful. If there are any questions that you didn't get to today, please feel free to submit them to the CDRH mailbox in the guidance, OncologyPilotCDRH@fda.hhs.gov.

Again, to summarize this pilot program is one step that might be helpful in reducing the risk of using unauthorized LDTs for oncology drug treatment decisions. And regarding the templates, our goal is

really to make the collection and provision of test validation and performance characteristic information as easy as possible when requested by FDA. So, thank you again for joining.

CDR Kim Piermatteo: Thanks McKenna for those final thoughts. To go over a few admin items, just for your information, printable slides of today's presentation are currently available on CDRH Learn at the link provided on this slide under the section titled In Vitro Diagnostics. A recording of today's webinar and a transcript will be posted to CDRH Learn under the same section in the next few weeks. And a screenshot of where you can find these webinar materials has been provided on the slide as well.

If you have additional questions about today's webinar, feel free to reach out to DICE at DICE@fda.hhs.gov. And lastly, we hope that you are able to join us for a future webinar. You can find a listing of all of our upcoming webinars via the link provided on the bottom of this slide at www.fda.gov/CDRHWebinar.

Thank you all again for joining us. This concludes today's CDRH webinar.

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