Final Rule: Medical Devices; Laboratory Developed Tests
May 14, 2024

Moderator: CDR Kim Piermatteo

CDR Kim Piermatteo: Hello, and thanks for joining us for today's CDRH webinar. 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.

We are holding this webinar to provide an overview of the final rule titled Medical Devices; Laboratory Developed Tests or LDTs, including a phaseout policy regarding LDTs. Today we will provide an overview of the final rule amending the FDA's regulations to make it explicit that in vitro diagnostic products, or IVDs, are devices under the Federal Food, Drug, and Cosmetic Act, including when the manufacturer of the IVD is a laboratory. We will also describe the phase out of the FDA's general enforcement discretion approach to LDTs.

Before we begin, I'd like to provide two reminders. First, please make sure you've joined us through the Zoom app and not through a web browser to avoid technical issues. And 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 FDA's Office of Media Affairs at FDAOMA@fda.hhs.gov.

I'd now like to introduce today's presenter, Elizabeth Hillebrenner, Associate Director for Scientific and Regulatory Programs in the Office of the Center Director within CDRH. We'll begin with a presentation from Elizabeth and then address your previously emailed questions about today's topic.

Thank you all again for joining us. I'll now turn it over to Elizabeth.

Elizabeth Hillebrenner: Thanks, Kim, and good afternoon all. Before diving into the rule itself, I'd like to take a minute on the background starting in 1976, when the medical device amendments amended the Federal Food, Drug, and Cosmetic Act to create a comprehensive system for the regulation of devices intended for human use.

In implementing the medical device amendments, FDA has exercised enforcement discretion such that it generally has not enforced applicable regulatory requirements for laboratory developed tests, including requirements related to registration and listing, reporting of adverse events to FDA, current good manufacturing practices, and premarket review of tests by FDA prior to use of the LDT in patient care, among other requirements.

What is a laboratory developed test or an LDT? FDA has generally considered a laboratory developed test to be an in vitro diagnostic that is intended for clinical use and designed, manufactured, and used within a single laboratory that is certified under CLIA and meets the regulatory requirements under CLIA to perform high complexity testing.

The rationale for the enforcement discretion approach was that at the time of passage of the Medical Device Amendments in 1976, LDTs were mostly manufactured in small volumes by laboratories that served their local communities. They tended to employ manual techniques and did not use automation.

They tended to be performed by laboratory personnel with specialized expertise and used and interpreted by physicians or pathologists in a single institution responsible for the patient and who were actively involved in patient care.

They tended to be manufactured using components legally marketed for clinical use, such as general purpose reagents or immunohistochemical stains marketed in compliance with FDA requirements. They were typically intended for use in diagnosing rare diseases or for other uses to meet the needs of a local patient population, or were generally similar to well characterized standard IVDs.

However, the LDT landscape has evolved significantly over the last almost 50 years. Today, IVDs offered as LDTs are often run in high volume for large and diverse populations. They increasingly rely on high tech or complex instrumentation and software to generate results in clinical interpretations. They are often used in laboratories outside of the patient's health care setting. Many LDTs are manufactured by laboratory corporations that market them nationwide as they accept specimens from patients across the country and run their LDTs in very large volumes in a single laboratory.

Today's LDTs are also more commonly manufactured with instruments or other components not legally marketed for clinical use. They are also more often used to inform or direct critical treatment decisions to widely screen for common diseases, to predict personal risk of developing certain diseases, and to diagnose serious medical conditions such as cancer and heart disease.

The risks associated with most LDTs today are therefore much greater than they were at the time FDA began implementing the Medical Device Amendments. For example, as LDTs increasingly rely on high tech instrumentation and software, the potential for cybersecurity vulnerabilities is growing. Many LDTs today are similar to other IVDs that have not been under FDA's general enforcement discretion approach.

As a result of these evolutions in the testing landscape, FDA has long recognized the need for a change in the Agency's general enforcement discretion approach for LDTs. Over the past few years, FDA has accumulated even more information supporting the need for change.

In light of these developments, FDA is amending FDA's regulations to make explicit that IVDs are devices under the Food, Drug, and Cosmetic Act, including when the manufacturer is a laboratory. FDA is also issuing a policy under which FDA is phasing out its general enforcement discretion approach for LDTs so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs. And FDA is adopting targeted enforcement discretion policies for specific categories of IVDs manufactured by laboratories.

The phaseout policy does not apply to tests that were excluded from our general enforcement discretion approach. FDA expects the following tests will continue to comply with applicable device requirements. First, tests that are intended as blood donor screening or human cells, tissues, and cellular and tissue-based product donor screening test required for infectious disease testing or required for determination of blood group and Rh factors.

Second, tests intended for emergencies, potential emergencies, or material threats declared under Section 564 of the Federal Food, Drug, and Cosmetic Act. Third, direct to consumer tests intended for consumer use without meaningful involvement by a licensed health care professional.

Additionally, tests manufactured and offered for use exclusively for public health surveillance are also not affected by the phaseout policy. The results of these tests are generally used for trending on a population basis or in public health outbreaks, where the test results are not intended for individual clinical decision making. Where test results are not reported to patients or their health care providers, they are not informing the care of that patient, and increased FDA oversight is less critical. Note that screening tests are distinct from public health surveillance tests, and screening tests do fall within the phaseout policy.

While FDA's general enforcement discretion approach has been focused on LDTs, we have determined to apply a broader scope for the phaseout policy consistent with our notice of proposed rulemaking. Specifically, the phaseout policy applies to IVDs that are manufactured and offered as LDTs by labs that are certified under CLIA and meet the regulatory requirements under CLIA to perform high complexity testing and that are used within such labs, even if those IVDs do not fall within FDA's traditional understanding of an LDT because they may not be designed, manufactured, and used within a single lab. For example, this may include a test designed in one lab and used in multiple labs.

FDA is adopting this scope because we recognize that not all labs have understood the limited nature of FDA's general enforcement discretion approach and have been offering IVDs based on the approach even when those IVDs do not fit what generally FDA would consider to be an LDT. This approach will help facilitate uniform compliance going forward.

FDA is phasing out its general enforcement discretion approach for LDTs in stages. Our intent is that following a four-year phase out period, IVDs offered as LDTs generally will be expected to meet applicable requirements according to the following timeline. Beginning May 6, 2025, FDA will expect compliance with medical device reporting requirements, for correction and removal reporting requirements, and complaint files.

Beginning May 6, 2026, FDA will expect compliance with requirements not covered during the other stages of the phase out policy, including registration and listing, labeling requirements, and investigational use requirements. Beginning May 6, 2027, FDA will expect compliance with quality system requirements not required in earlier stages. Note that for LDT specifically, FDA expects compliance with the following elements of the quality system regulations: design controls, purchasing controls, acceptance activities, CAPA, and records requirements.

Beginning November 6, 2027, FDA will expect compliance with premarket review requirements for high risk IVDs offered as LDTs. Beginning May 6, 2028, four years after the publication date of this final rule, FDA will expect compliance with premarket review requirements for moderate risk and low risk IVDs offered as LDTs. Note, however, that most low risk IVDs are exempt from premarket review.

For several categories of tests, FDA intends to continue the general enforcement discretion approach and generally not enforce any applicable requirements, because tests in these categories are, in our experience, unlikely to pose significant risks or are conducted in circumstances that themselves will mitigate the risks. Tests in these categories are 1976 type LDTs.

These tests have the following characteristics common among LDTs offered in 1976. The use of manual techniques without automation performed by laboratory personnel with specialized expertise. Use of

components legally marketed for clinical use. Design, manufacture, and use within a single CLIA certified lab that meets the requirements under CLIA for high complexity testing.

Another category are certain Human Leukocyte Antigen or HLA tests for transplantation. These tests include HLA tests that are designed, manufactured, and used within a single lab certified under CLIA that meets the requirements to perform high complexity histocompatibility testing when used in connection with organ, stem cell, and tissue transplantation to perform HLA allele typing for HLA antibody screening and monitoring, or for conducting real and virtual HLA crossmatch tests.

Another category are forensic tests. These tests are intended solely for forensic or law enforcement purposes. Another category based on comments received in the docket are Department of Defense and Veterans Health Affairs LDTs. These are LDTs manufactured and performed within the VHA or the DOD. This policy applies only to LDTs used for patients that are being tested and treated within the DOD or VHA.

Based on consideration of comments received in the docket following our notice of proposed rulemaking, FDA generally intends to exercise enforcement discretion with respect to premarket review requirements for the following two categories of tests. First, we have LDTs that are approved, including conditionally approved or within an approved exemption from full technical documentation under the New York State Department of Health's Clinical Laboratory Evaluation Program or CLEP.

Now, FDA is aware that some labs may offer different versions of an LDT depending on whether a patient specimen comes from New York State or from elsewhere. To be clear, FDA's enforcement discretion policy here applies only to the version of the test approved by New York State CLEP.

Second, we have certain FDA authorized IVDs modified by and performed within a CLIA compliant lab. This policy applies when a laboratory certified under CLIA and meeting the regulatory requirements under CLIA to perform high complexity testing modifies another manufacturer's 510(k) cleared or De Novo authorized test, following design controls and other quality system requirements for which FDA expects compliance, in a manner that could not significantly affect the safety or effectiveness of the test. It does not constitute a major change or modification in intended use and where the modified test is performed only in the laboratory making the modification.

On the right-hand side of the slide, you can see the requirements with which FDA expects compliance for these tests. These include the requirements in stages one to three of the phaseout policy as outlined earlier in this presentation.

So based on consideration of comments received in the docket following our notice of proposed rulemaking, FDA intends to exercise enforcement discretion and generally not enforce premarket review and most quality system requirements, with the exception of records requirements, for three categories of tests.

First, we have LDTs manufactured and performed by a laboratory integrated within a health care system to meet an unmet need of patients receiving care within the same health care system. Second are currently marketed IVDs offered as LDTs that were first marketed prior to May 6, 2024, which is the date of issuance of the final LDT rule, as long as they are not modified after that date or are modified but only in certain limited ways that do not change the indications for use, alter the operating principle of the

IVD, includes significantly different technology, or adversely change the performance or safety specifications of the IVD.

The last category here includes certain non-molecular antisera LDTs for rare red blood cell antigens for transfusion compatibility, when such tests are manufactured and performed by blood establishments, including transfusion services and immunohematology laboratories, and when there is no alternative IVD available to meet the patient's need for a compatible blood transfusion. Note that this policy does not apply to molecular tests used for genotyping red blood cell antigens.

Now, on the right-hand side of the slide, again, you can see the requirements with which FDA expects compliance for these tests. They include the requirements in stages one to two of the phaseout policy, as outlined earlier in this presentation, as well as records requirements under stage three.

That wraps up my overview of the final rule and phaseout policy. We believe it will better protect the public health by helping to assure the safety and effectiveness of IVDs offered as LDTs, while also accounting for other public health considerations, such as patient access and reliance.

FDA intends to hold additional webinars on specific aspects of the final rule, targeted enforcement discretion policies, and other matters applicable to IVDs, including LDTs. Next up is a webinar on the Draft Guidances on Immediate Response Tests and Enforcement Discretion in the Context of a 564 Declaration. This webinar is scheduled for June 5, 2024 at 1:00 PM. Please submit your questions in advance of the webinar to the mailbox provided.

Finally, I would like to leave you with some links to available resources, recognizing that additional resources will be forthcoming.

Thanks for your time today, and I will hand things back to Kim to kick off our Q&A.

CDR Kim Piermatteo: Thank you, Elizabeth, for your presentation. At this time, we'll now transition to addressing some of your previously submitted questions related to the final rule. Thank you to everyone who submitted questions in advance of today's webinar. For this segment, Elizabeth and I will provide a back and forth and I'll read a question aloud and then Elizabeth will provide a response.

I would like to remind everyone that we will have our next IVD related webinar on June 5, like Elizabeth mentioned, addressing the two draft guidance documents that issued concurrently with the final rule. And we also intend to hold additional webinars focused on specific topics related to the phaseout policy. Therefore, some of your questions may be addressed during one of these future webinars. And you will have additional opportunities to submit questions in advance for possible discussion during these webinars. And those details will be announced. So I encourage you to refer to FDA's LDT webpage, specifically the section on webinars, for information on future webinar dates and topics.

If you have additional questions after today's webinar about the final rule specifically, you may send an email to LDTFinalRule@fda.hhs.gov.

One last reminder also. We will not be taking live questions today, so please refrain from raising your hand in Zoom. So let's get started. We intend to address many of your previously submitted questions today.

So, Elizabeth, our first question is related to what is and what is not an LDT. And that question has two parts. That question is, if another manufacturer's FDA authorized IVD is modified by a laboratory manufacturer, including a modification for use on a new patient population, is that IVD an LDT? Additionally, if a health care provider orders an IVD for use that is outside the IVD's authorization for an individual patient, is that IVD an LDT?

Elizabeth Hillebrenner: Thanks, Kim. These are good questions. So as discussed in the preamble to the LDT final rule, an LDT is an IVD that is intended for clinical use and is designed, manufactured, and used in a single high complexity CLIA lab. This definition does not exclude previously FDA authorized IVDs that are modified by a lab for a use that is outside the IVD's original authorization. So here I would refer to the preamble to the final rule for discussion of the phaseout policy, which includes targeted enforcement discretion policies such as those relating to mods, modifications, of an FDA authorized IVD and to LDTs for unmet needs.

Now, when a health care provider orders an IVD for a use that is outside the IVD's authorization, that does not dictate whether the IVD is an LDT or not. In other words, it doesn't dictate whether it is designed, manufactured, and used within that single high complexity CLIA lab.

We note that under the Food, Drug, and Cosmetic Act, a health care practitioner may prescribe or administer a legally marketed device to a patient for any condition or disease within a legitimate health care practitioner patient relationship. And this could include situations where the health care practitioner specifically orders the use of an IVD outside of its original authorization for an individual patient. So I hope that helps with those questions, Kim.

CDR Kim Piermatteo: Thanks, Elizabeth. So another question related to what is and what is not an LDT is, if a single laboratory designs and manufactures an IVD but uses the IVD at different subsidiaries, is the IVD an LDT? If not, how would FDA treat these IVDs?

Elizabeth Hillebrenner: Another good question. So again, LDTs are in vitro diagnostic products intended for clinical use that are designed, manufactured, and used in a single high complexity CLIA lab. So if an IVD is designed, manufactured, or used in more than one lab, it is not an LDT.

However, our phaseout policy described in the preamble to the final rule applies to IVDs offered as LDTs. And so these are IVDs that are manufactured and offered as LDTs, again, by labs that are certified under CLIA for high complexity testing even if these IVDs do not fall within FDA's traditional understanding of an LDT because they are not designed, manufactured, and used within a single lab.

And we adopted this scope, as I explained, because it recognizes that not all labs have understood the limited nature of our general enforcement discretion approach, and some have been offering IVDs based on the approach, even when their IVDs do not fit what FDA considers to be an LDT. And so the other thing to keep in mind here, though, is that the targeted enforcement discretion policies for certain new LDTs introduced after May 6 of this year are limited to LDTs as defined by FDA.

CDR Kim Piermatteo: Thanks, Elizabeth. Now I'd like to ask a question that was previously submitted related to modifications. And that question is, how does FDA intend to treat modifications to IVDs offered as LDTs that fall within the enforcement discretion policy for currently marketed IVDs offered as

LDTs under the final rule?

Elizabeth Hillebrenner: OK Kim, so as we discussed in the phaseout policy in the preamble, we do not expect compliance with premarket review and most quality system requirements for currently marketed IVDs offered as LDTs as long as they are not modified following issuance of the final rule on May 6 or if they are modified, only in certain limited ways. So we generally expect compliance with premarket review and quality system requirements for the currently marketed IVDs when modifications are made to them that either change the indications for use, alter the operating principle of the IVD, include significantly different technology, or adversely change the performance or safety specifications of the IVD.

So one thing that we saw come up in several questions was about instrument replacement. So for this example where a laboratory does routine instrument replacement on an IVD currently marketed, IVD offered as an LDT, it may continue to fall within this enforcement discretion policy if the modified version with the new instrument does not fall within any of the circumstances I just listed.

CDR Kim Piermatteo: Thanks, Elizabeth. Next, we have a few questions related to small laboratories. So I'll read all these questions and then I'll turn it over to you, Elizabeth.

Elizabeth Hillebrenner: Sounds good.

CDR Kim Piermatteo: So some of the questions are, under the phaseout policy, does FDA intend to treat small laboratories differently? How will FDA ensure that small laboratories will be able to continue developing and offering innovative tests? Will the submission requirements for an LDT manufactured by a small laboratory be the same as for an LDT manufactured by a large entity?

Elizabeth Hillebrenner: OK. Lots of good questions. So as we explained in the preamble to the final rule, we do recognize that some small labs may be disproportionately impacted by the phaseout of our general enforcement discretion approach for LDTs from a financial perspective. However, the final phaseout policy includes several enforcement discretion policies that we believe anticipate will reduce costs for labs, including for small labs.

So, for example, these include the targeted enforcement discretion policies with respect to currently IVDs offered as LDTs currently marketed or marketed prior to May 6, as well as LDTs manufactured and performed by a laboratory integrated within a health care system to meet an unmet need of patients receiving care within the same health care system.

We do note that premarket submission requirements for IVDs do not depend on the manufacturer of the IVD. So for example, it doesn't matter, the requirements don't change based on whether they are a laboratory or a non-laboratory manufacturer, nor based on the size of the manufacturer. So I hope that helps with those questions, Kim.

CDR Kim Piermatteo: Thanks, Elizabeth. Next, we received some questions related to rare diseases and unmet needs. The first question that we received was, is there an enforcement discretion policy for LDTs for rare diseases or smaller patient populations?

Elizabeth Hillebrenner: Great question. So we recognize the challenges faced by patients with rare diseases, their families, and their treating physicians as well. We also recognize that IVDs offered as LDTs play an important role in health care and may address various unmet needs, including for rare diseases. So we believe that several of the enforcement discretion policies adopted in the phaseout policy will help address the availability of IVDs for unmet needs in rare diseases.

These include, for example, our intent to exercise enforcement discretion with respect to premarket review and quality system requirements for currently marketed IVDs offered as LDTs. Also, our intent to exercise enforcement discretion and generally not enforce premarket review and quality system requirements for LDTs manufactured and performed by a lab integrated within a health care system to meet an unmet need of patients receiving care within the same health care system. This policy is intended, among other things, to address situations where there is no available FDA authorized IVD for the disease or condition, which may be the case for rare diseases or smaller patient populations.

We also recognize that it can be challenging to validate tests for rare diseases or smaller patient populations where it is difficult to obtain clinical samples. FDA intends to consider whether issuing additional guidance regarding validation of tests, including those for rare diseases, that takes into consideration the challenges in obtaining a robust number of samples for validation would be helpful.

CDR Kim Piermatteo: Thanks, Elizabeth. So another question related to this topic, two questions actually, what qualifies as a rare disease? And is there a list or specific criteria that FDA plans on using?

Elizabeth Hillebrenner: OK, so as discussed in the preamble, we did not adopt an enforcement discretion policy for LDTs for rare diseases, per se. I note that the Food, Drug, and Cosmetic Act that there is a threshold for Humanitarian Use Designation, HUD designation, for a device, and this includes IVDs that are offered to no more than 8,000 patients across the U.S. per year.

However, our phaseout policy does include other enforcement discretion policies for certain LDTs for unmet needs, which may include LDTs for rare diseases. We intend to exercise enforcement discretion with respect to premarket review and quality system requirements for LDTs manufactured and performed by a lab, integrated within a health care system to meet an unmet need of patients receiving care within that same health care system.

We consider an LDT to be for an unmet need where there is no available FDA authorized IVD that meets the patient's need, which may include circumstances where there is no FDA authorized IVD for a rare disease or condition. We intend this policy to be targeted. It's not intended to serve as an alternative pathway to market for LDTs for unmet needs. And we also intend to provide additional guidance on this enforcement discretion policy in the future.

CDR Kim Piermatteo: Thanks, Elizabeth. So one last question on this rare disease topic, and that is, if a laboratory integrated within a health care system offers an LDT to meet an unmet need of patients receiving care in the health care system, is the laboratory's ability to offer that LDT impacted by FDA authorization of a different IVD for that unmet need?

Elizabeth Hillebrenner: So if there is no longer an unmet need for an LDT, because in this example, FDA authorizes an IVD that meets the needs of the patient, then the LDT would no longer fall within this enforcement discretion policy. However, if the new IVD that receives authorization for the same

indication as an LDT offered as described in this policy, if the new IVD is offered in another health care system that is not accessible to the patient and the laboratory manufacturing the new IVD does not make it available outside its system, then the new FDA authorized IVD would not be available to the patient and the LDT would continue to be an LDT for an unmet need.

CDR Kim Piermatteo: Great. Thanks, Elizabeth. Alright, now we're going to move on to a question that is related to enforcement discretion policies with respect to all FDA requirements. And so the question asked is, does the final rule apply to a forensic use only drug test for hospital use?

Elizabeth Hillebrenner: OK, so for tests that are intended solely for forensic or law enforcement purposes, we intend to exercise enforcement discretion and generally not enforce any applicable requirements. And FDA has actually had such policy for these tests for over 20 years and has applied this approach regardless of whether the tests for forensic purposes are offered as LDTs or not.

That's because tests used in law enforcement are subject to protections and requirements that mitigate risk related to test accuracy and sample collection. Now, an LDT that is used for forensic and other purposes does not fall within that policy, though it may fall within other targeted enforcement discretion policies described in the preamble to the final rule.

CDR Kim Piermatteo: Thanks again, Elizabeth. OK, so now I have a few questions related to the continued enforcement discretion for currently marketed tests. The first question is, are there any enforcement discretion policies that apply if a laboratory makes changes to another manufacturer's test?

Elizabeth Hillebrenner: Good question. So as we discussed in the preamble, we do not intend to enforce premarket review requirements for certain laboratory changes to another manufacturer's lawfully marketed test. This policy applies when a high complexity CLIA lab modifies another manufacturer's test that's either 510(k) cleared or De Novo authorized, following design controls and other quality system requirements for which FDA expects compliance in a manner that could not significantly affect the safety or effectiveness of the test, and does not constitute a major change to the intended use, and where the modified test is performed only in the lab that's making the modification.

We expect premarket submissions from labs modifying a third-party's cleared or authorized test for the same types of changes for which FDA would expect a premarket submission from the original manufacturer modifying its own test. And we're adopting this policy really to promote more efficient and effective use of agency resources and also because we understand that labs may make such changes, for example, to integrate a test into its operations, to accommodate local conditions, or address supply shortages.

So taking into account the risks associated with the relatively minor changes to 510(k) cleared or De Novo authorized tests when they occur in a single lab without broad distribution, at this time, we believe the resources needed to review these types of changes can generally be better spent on other agency priorities and activities.

But this is not the same calculus when it comes to higher risk tests. And so we are not applying this enforcement discretion policy to modifications to another manufacturer's PMA approved or BLA

licensed tests, because such tests are high risk and changes to such tests pose corresponding increased risks.

We also note that there's just relatively few IVDs that are high risk today, and we anticipate even fewer in the future based on our intent to reclassify most class III IVDs into class II. So therefore, we anticipate that these tests present resource considerations that are just different from those of the moderate risk test that led to this policy.

CDR Kim Piermatteo: Thanks, Elizabeth. That was a great response. Another question that we have related is, are manual LDTs that were first marketed prior to May 6 of 2024, are they grandfathered in?

Elizabeth Hillebrenner: OK. I appreciate the chance to clarify this, Kim. The rule does not, quote, "grandfather" any IVDs. If an IVD was offered as an LDT prior to May 6 of this year and is not modified in a way that changes its indications for use, alters the operating principle, includes significantly different technology, or adversely changes the performance or safety specs, then we intend to exercise enforcement discretion and generally not enforce premarket review and most quality system requirements. This enforcement discretion policy is not limited to manual tests.

Additionally, for tests that have certain characteristics that are common among LDTs offered in 1976, we intend to exercise enforcement discretion with respect to all applicable requirements. The characteristics of tests under this enforcement discretion policy are that they use manual techniques without automation performed by lab personnel with specialized expertise. They use components legally marketed for clinical use, and they're designed, manufactured, and used in a single high complexity CLIA lab.

The enforcement discretion policies for 1976 type tests and for currently marketed IVDs operate as LDTs are separate policies, although some tests may fall under both. And just to clarify, too, as mentioned in the presentation and in the preamble, certain donor screening tests, tests intended for emergencies, potential emergencies or material threats under 564, and direct to consumer tests are excluded from the scope of the phaseout policy, and FDA continues to expect compliance with applicable requirements for such tests, regardless of whether they would otherwise fall within an enforcement discretion policy described in the preamble. So I hope that helps to clarify.

CDR Kim Piermatteo: Great. Thanks, Elizabeth. So at this time, we've addressed many questions so far. I would just like to remind all of our attendees that we will be providing a presentation recording and a transcript. That way you can go back and see these questions and the responses that are being provided. And we hope to get those up as soon as we can after today's webinar. So look for those.

OK, Elizabeth, we're going to move on to a question related to IVDs being offered as LDTs by public health laboratories. And that question is public health laboratories, or PHLs, perform diagnostic tests as a service to state and local governments and may use LDTs validated under CLIA. Does the final rule impact public health laboratories' use of such LDTs?

Elizabeth Hillebrenner: Great question. So FDA appreciates the important role that public health labs play in our health care system. And the final rule does not provide a separate policy for LDTs manufactured and offered by public health labs, but various enforcement discretion policies that are detailed in the preamble to the final rule may be applicable to IVDs offered as LDTs by public health labs.

These include, for example, enforcement discretion with respect to premarket review and most quality system requirements for currently marketed IVDs offered as LDTs as well as enforcement discretion with respect to premarket review for LDTs approved, conditionally approved, or within an approved exemption from full technical documentation under New York State's CLEP program.

I would also add that we have issued draft guidance describing a proposed enforcement discretion policy for certain immediate response tests designed, manufactured, and used within state or local public health labs, among other entities. And we're seeking comment on this proposal currently prior to issuing final guidance, and this will be discussed in our next webinar.

CDR Kim Piermatteo: Great. Looking forward to that next webinar. So another question we received is regarding the impact on tests currently being developed. And the question came in as how does the final rule affect laboratories that are currently developing IVDs which will not be marketed prior to the date of issuance of the final rule?

Elizabeth Hillebrenner: Good question. So some IVDs manufactured and first offered by labs after the date of issuance, after May 6 of this year, may fall within a targeted enforcement discretion policy described in the preamble. And I would add that we have just posted this afternoon on our website a table to help manufacturers better understand the general expectations of IVDs falling within these different policies. I refer you to the preamble for complete details, but the table provides a high-level view of the different enforcement discretion policies.

Then the phaseout policy details when compliance with the different requirements would be expected. So as we reviewed in the presentation, in one year, May 6, 2025, we expect compliance with medical device reporting requirements, correction and removal reporting requirements, and complaint files. At two years, May 6, 2026. We expect compliance with requirements that are not covered during the other stages of the phase out policy, including registration and listing, labeling, and investigational use requirements.

Stage three is in 2027, and we expect compliance with quality system requirements. And note that for LDT specifically, we expect compliance only with design controls, purchasing controls, acceptance activities, CAPA, and records requirements at this time. And then premarket review would begin for high-risk tests in November 2027 and for moderate and low risk tests to which premarket review requirements apply in May of 2028.

I'd also add that we don't intend to enforce premarket authorization requirements after a complete PMA, 510(k) or De Novo has been submitted, if it's submitted on time according to this phaseout until we complete our review of the submission. Given that such IVDs that are introduced during this transition period may already be on the market and available to patients when they're coming into us for review, we do not intend to interrupt access at the point when a submission is made.

So IVDs for which a PMA, 510(k) or De Novo request is submitted prior to the applicable time frame will remain under enforcement discretion for the pendency of our review, whereas those that are submitted after the applicable time frame detailed in the phaseout policy would not fall within the enforcement discretion policy and FDA clearance or authorization would be expected prior to such test being offered.

CDR Kim Piermatteo: Thanks, Elizabeth. And that's great update information on that table being posted. So hopefully our attendees can take a look at that. Another question that we received regarding laboratory changes was, would an LDT first marketed prior to May 6, 2024 be viewed by FDA as a new LDT if the laboratory moves the location of the facility?

Elizabeth Hillebrenner: Good question. So if the same lab is offering the same LDT before and after publication of the final rule, the LDT generally would fall within the currently marketed IVD offered as an LDT policy, so long as the IVD is not modified, or modified in a way that does not change indications for use, alter the operating principle, include significantly different technology, or adversely change the performance or safety specs of the IVD.

CDR Kim Piermatteo: Great. Thanks, Elizabeth. Alright, so another question we have is are therapeutic drug monitoring or TDM, TDM LDTs covered by the final rule?

Elizabeth Hillebrenner: TDM tests, including mass spec based TDMs, are IVDs. So TDM tests manufactured by labs are covered by the final rule and the phaseout policy described in the preamble.

CDR Kim Piermatteo: Thanks. So another question is we received, FDA, we received numerous questions about whether specific tests may be considered a, quote, "1976 type test" for purposes of falling within the enforcement discretion policy, including tests such as the analyte specific reagent class I staining protocols, standard chromosome analysis, histopathology slides, cytology slides, karyotyping slides, peripheral blood smear screening, and fluorescence in situ hybridization of cytogenic cell preparations. Elizabeth, can you clarify if these tests are 1976 type tests?

Elizabeth Hillebrenner: OK, so in general, '76 type tests have the following characteristics. They use manual techniques without automation performed by lab personnel with specialized expertise. They use components legally marketed for clinical use. And they're designed, manufactured, and used in a single high complexity CLIA lab. So tests with these three characteristics generally fall within the 1976 type enforcement discretion policy.

FISH and IHC tests often have these three characteristics and in those cases would fall within the policy. Tests using automation, including automated staining methods, automated plate readers, or automated interpretation would not have the first characteristic, because they would not be considered manual techniques without automation. And they would not be in the policy.

And then tests with components that are labeled Research Use Only or RUO would not meet the second characteristic, because appropriately labeled RUO IVD products are not legally marketed for clinical use. So I hope that helps provide some clarity around this policy for 1976 type tests.

CDR Kim Piermatteo: Thanks, Elizabeth. Alright, let's talk about some FDA resources. So a question we received was, will FDA have sufficient resources to be able to implement the phased enforcement timeline?

Elizabeth Hillebrenner: So FDA considered resources in the development of the phaseout policy. In advance of the next-- so we have aligned the phaseout policy such that premarket review requirements align with the next user fee reauthorization process. And this alignment will give FDA and industry the opportunity to negotiate user fees with the knowledge that laboratory manufacturers generally will be

expected to comply with applicable requirements. Additionally, the enforcement policies announced in the rule and the additional information FDA will have about LDTs through registration and listing in stage two will also facilitate planning and efficient allocation of FDA's resources to best serve public health.

We also anticipate that labs may seek to utilize our third-party review program, which under our current user fee program, we are working to enhance, as well as predetermined change control plans that can reduce the number of future submissions for significant modifications to test that they have authorization, approval, or clearance for.

And then, as previously mentioned, we have announced our intent to reclassify most IVDs that are class III into class II and aim to complete this prior to stage four of the phaseout policy, which would allow manufacturers of certain types of tests to seek marketing clearance through the less burdensome 510(k) pathway. So we have really thought about resources in the development of this phaseout policy.

CDR Kim Piermatteo: Thanks, Elizabeth. So a similar related question is about timing. So how will premarket review of LDTs under this phaseout policy affect the review timelines for other IVDs?

Elizabeth Hillebrenner: So our premarket review timelines, like I alluded to before, are negotiated with industry in connection with our medical device user fee reauthorization process. And we generally meet timeframes for MDUFA decisions that are negotiated with industry, including for IVD submissions outside of our experience in the pandemic. And as previously mentioned, this process aligns with the timeline for reauthorization discussions around our next user fee cycle, providing an opportunity for us to negotiate fees and goals for premarket reviews with our stakeholders.

CDR Kim Piermatteo: Thanks, Elizabeth. Another question related to timing is also are the stages of the phaseout policy measured from the publication date or the effective date of the final rule?

Elizabeth Hillebrenner: The timelines for the phaseout policy are set based on the publication date of May 6, 2024.

CDR Kim Piermatteo: Thanks, Elizabeth. Alright. So we have about five minutes left. We're going to try to get to a few more questions before we close out today. So let's move on to some questions related to the New York state's CLEP program.

One of these questions is, do LDTs with the New York State's CLEP approval fall within an enforcement discretion policy in the phaseout policy? What if another lab offers an LDT that is not approved by the New York State CLEP, but is similar to an LDT approved by the New York State CLEP? Would it fall within the enforcement discretion policy for LDTs approved by the New York State CLEP?

Elizabeth Hillebrenner: OK, so we intend to exercise enforcement discretion with respect to premarket review for LDTs that are approved, conditionally approved, or within an approved exemption from full technical documentation by New York CLEP. As described in the preamble, this policy applies to the version of the LDT approved by New York. Therefore, if a test is not approved by New York, it would not be in this policy.

CDR Kim Piermatteo: Thanks, Elizabeth. Another question related to the New York State CLEP is, does this mean LDTs approved by the New York State CLEP are not generally expected to comply with any FDA requirements?

Elizabeth Hillebrenner: No, that's not what it means. We intend to exercise enforcement discretion only with respect to premarket review requirements for LDTs in this policy. So for other applicable requirements, including, for example, medical device reporting, corrections and removals, labeling, quality systems, we intend to phase out the general enforcement discretion approach consistent with the stages described in the preamble.

CDR Kim Piermatteo: Great. So one more question related to the New York State CLEP. What is the difference between an LDT that is approved, conditionally approved, or within an approved exemption from full technical documentation by the New York State CLEP and an LDT that is currently marketed prior to May 6, 2024.

Elizabeth Hillebrenner: OK, so for currently marketed IVDs offered as LDTs, the ones that are marketed prior to May 6, we intend to exercise enforcement discretion with respect to both premarket review and most quality system requirements. Now, for new IVDs offered as LDTs that weren't marketed prior to May 6, we expect compliance with applicable requirements, premarket review, quality system, et cetera, consistent with the stages in the preamble.

However, if such a new IVD falls within an enforcement discretion policy described in the preamble, we intend to exercise enforcement discretion as described in that policy. Now, the New York policy relates to general enforcement discretion with respect to premarket review requirements. So that is the difference here.

CDR Kim Piermatteo: Great. Thanks, Elizabeth. I think we have time to address one more question today. And that question is, will FDA be providing additional webinars and/or guidance on specific topics?

Elizabeth Hillebrenner: Yes, absolutely. And I should mention, too, that sort of foundational to our approach here is ensuring that we're answering generally applicable questions in a manner that is transparent to the entire industry. And so to that end, we intend to hold additional webinars that are accessible to everybody.

And we'll consider providing additional guidance and/or additional resources on specific topics, such as compliance with applicable labeling requirements over the course of the phaseout period. And to the extent that we do issue additional guidance, we would, of course, do so in accordance with our good guidance practice regulations, giving folks opportunity for comment before they are finalized.

CDR Kim Piermatteo: Thanks, Elizabeth. So that wraps up our previously submitted questions for today. And I think I'd like to turn it back over to you, Elizabeth, to provide your final remarks for today.

Elizabeth Hillebrenner: Thanks, Kim. I'd just like to close with thanking our stakeholders for their comments to the docket. We got over 6,500 comments, very thoughtful, very constructive, and they were very helpful in our development of the final rule and the phaseout policy described in the preamble. And we believe that this final rule, including the phaseout policy, will better protect the

public health by helping to assure the safety and effectiveness of IVDs offered as LDTs while also accounting for other important public health considerations, such as patient access and reliance. And we really look forward to working with our stakeholders as we move forward with smooth implementation.

CDR Kim Piermatteo: Thanks again, Elizabeth, and thanks for those final remarks. For everyone's information, printable slides of today's presentation are currently available on CDRH Learn and on the actual link for this webinar. And the link for CDRH Learn though, is provided on this slide. And you can find this material under the section titled In Vitro Diagnostics within CDRH Learn.

As I mentioned previously, a recording of today's webinar and a transcript will be posted to the webinar page as well as to CDRH Learn in the next few weeks. A screenshot of where you can find these webinar materials, like I said, is provided on this slide.

Also mentioned earlier, if you have additional questions about this final rule that were not addressed today, you may send an email to LDTFinalRule@fda.hhs.gov. And if you have additional questions about today's webinar in general, feel free to reach out to us at DICE, at dice@fda.hhs.gov.

And then lastly, just as a reminder, Elizabeth mentioned, we hope you're able to join us for our June 5 webinar on the Draft Guidances on Immediate Response Tests and Consideration of Enforcement Policies for Tests in the Context of a 564 Declaration. You can find information on how to attend any of our upcoming webinars on our CDRH events page, and the link to this page is provided on the bottom of this slide.

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

****

END