Proposed Rule: Medical Devices; Laboratory Developed Tests
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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 your moderator for today's webinar.

We are holding this webinar to provide information on the Proposed Rule Regarding Laboratory Developed Tests, or LDTs. Today, we will provide an overview of the rulemaking proposal to amend the FDA's regulations to make 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. And we will describe the proposed phaseout of 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 any 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 the 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. FDA's proposed rule that we are discussing today is aimed at helping to ensure the safety and effectiveness of laboratory developed tests, or LDTs. It can be found in the Federal Register at the link provided.

Before diving into the proposed rule itself, I'd like to take a minute on the role of in vitro diagnostic devices in our health care. Diagnostic testing is truly a cornerstone of modern medicine. The CDC estimates that 70% of medical decisions are based on lab test results. So given the role tests play in modern medical care, their validity has a significant impact on the public health.

Where a test provides a false positive result-- in other words, where a patient is told they have a disease or a condition that they do not actually have-- this can delay diagnosis and treatment of the true disease or condition, lead to unwarranted interventions, and cause distress. Now, those unwarranted interventions could include medications with serious side effects or risky medical procedures. On the other hand, if a test provides a false negative result-- that is where the patient may be told that they do not have a disease or a condition that they actually do have-- this can lead to progression of disease, in some cases without the opportunity for lifesaving saving treatment and in other cases could lead to the spread of infectious disease.

So the harms to patients from false-positive and false-negative results can be significant. For example, where a patient with cancer receives a false-positive for a particular biomarker, this can result in the

application of an ineffective treatment that has negative side effects and does not stop the progression of the cancer. False-negative results can also be fatal when they lead to a failure to use a lifesaving medication. Thus, the accuracy of lab tests is critical to our healthcare.

Many tests used in the application of health care across the US are laboratory developed tests or LDTs. FDA has traditionally considered an LDT to be an IVD that is intended for clinical use and that is designed, manufactured, and used within a single CLIA-certified laboratory that meets the regulatory requirements under CLIA to perform high complexity testing. IVDs, including LDTs, are devices under Section 201(h)(1) of the Federal Food, Drug, and Cosmetic Act. In implementing the medical device amendments of 1976, the FDA adopted a general enforcement discretion approach for LDTs, such that it generally has not enforced applicable regulatory requirements for most LDTs.

At that time, in 1976, LDTs were mostly manufactured in small volumes by local labs. 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 tests. They also tended to employ manual techniques performed by laboratory personnel without automation and be manufactured using components legally marketed for clinical use among other things.

Over the past half century, the LDT landscape has evolved. Today, many LDTs rely on high tech or complex instrumentation and software to generate results in clinical interpretations. They are often used in labs outside of the patient's health care setting and are often manufactured in high volume for large and diverse populations. Many LDTs are manufactured by laboratory corporations that market the tests nationwide, as they accept specimens from patients across the country and run their LDTs in very large volumes in a single lab.

Today's LDTs are also more commonly manufactured with instruments or other components not legally marketed for clinical use and are 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.

FDA is aware that this scheme is, in some cases, fostering unfounded claims of innovation rather than responsible innovation. These claims are concerning to FDA because they can mislead the public, undermine legitimate competition, and disincentivize responsible science-based innovation. Applying the same oversight approach to labs and non-labs that manufacture IVDs would better assure the safety and effectiveness of LDTs and would remove a disincentive for non-laboratory manufacturers to develop novel tests.

As a result of this evolution in the testing landscape, FDA has long recognized the need for a change in the agency's general enforcement discretion approach for LDTs. Many test systems made by laboratories today are functionally the same as those made by other manufacturers of IVDs.

IVDs offered as LDTs have a significant impact on modern medical care. They comprise a growing sector of the diagnostic testing market and are proliferating in some of the most complicated and sensitive areas of medical practice where the presence of a valid test can be most important. Sometimes they use complex algorithms to calculate scores for diagnosis with little transparency to the user about the basis for these algorithms. In many cases, these IVDs are intended to inform drug treatment, directing physicians to choose certain drugs based on a patient's genetic or other information.

Current information raises serious questions about whether patients can rely on IVDs offered as LDTs. Back in 2015, we had published a report of 20 case studies involving inaccurate, unsafe, ineffective, or poor quality LDTs that caused or may have caused patient harm. More recent evidence suggests that the situation is getting worse. This evidence cuts across test types and laboratories and is from a variety of sources, including published studies in the scientific literature, allegations of problematic tests reported to FDA, FDA's own experience in reviewing IVDs offered as LDTs, news articles and class action lawsuits. Overall, the evidence points to fundamental uncertainty in the marketplace about whether IVDs offered as LDTs provide accurate and reliable results.

This brings us to the proposed rule. We are proposing to amend regulations to make explicit that IVDs are devices under the Federal Food, Drug, and Cosmetic Act, including when the manufacturer of the IVD is a laboratory. The preamble describes a proposed phaseout of FDA's general enforcement discretion approach. It is designed to increase oversight of LDTs in line with our public health mission. FDA seeks public comment on the proposed amendment and the matters discussed in the preamble and the preliminary regulatory impact analysis or the PRIA.

The proposed phaseout of enforcement discretion spans five stages over the course of four years following publication of the final phaseout policy as outlined in the summary table.

One year from publication of the final phaseout policy, we would phaseout enforcement discretion for medical device reporting requirements. This refers to reporting of adverse events to FDA, as well as correction and removal reporting requirements.

Then two years from publication of the final phaseout policy, we would phaseout enforcement discretion for all requirements other than those identified in the other stages. This includes requirements for registration and listing, labeling and investigational use.

Three years from publication of the final phaseout policy, we would phaseout enforcement discretion for Quality System requirements. Here, we are proposing to leverage some assurances provided by CLIA and tailoring the Quality System requirements for situations in which all manufacturing activities occur within a single lab, and the IVD is not distributed outside of that lab. In such situations, FDA would expect compliance with design controls, purchasing controls, acceptance activities, corrective and preventive actions, and records requirements.

Stage 4 would commence three and a half years from publication of the final phaseout policy but not before October 1, 2027. At this time, we begin to phaseout premarket review requirements starting with high-risk tests. Note that October 1, 2027, marks the beginning of a new user fee cycle. This alignment would provide an opportunity for industry participation in negotiations regarding the next user fee cycle with the knowledge that laboratory manufacturers would be expected to comply with premarket review requirements.

Stage 5 would follow at four years from publication of the final phaseout policy but not before April 1, 2028. This would include premarket review for moderate risk tests and those low-risk tests for which premarket review is required. For all tests for which a premarket submission has been made pursuant to the phaseout policy in Stages 4 and 5, FDA generally would not intend to enforce until FDA completes its

review of the application. Given that such IVDs may already be on the market and available to patients, FDA generally does not intend to interrupt access at the point when a submission is made.

In the notice of proposed rulemaking, we have identified three categories of tests for which we have generally expected applicable requirements to be met. In other words, these categories of tests have generally not been part of our enforcement discretion approach for most LDTs. These categories of tests include those that are intended to screen donors of blood, human cells, tissues, and cellular and tissue-based products for infectious diseases or for determination of blood group and Rh factors, tests intended for emergencies, potential emergencies, or material threats declared under Section 564 of the Federal Food, Drug, and Cosmetic Act, and direct to consumer tests intended for consumer use without meaningful involvement by a licensed health care professional. For all of these categories of tests, we currently expect compliance with applicable requirements.

In the notice of proposed rulemaking, we have also identified categories of tests that would not be affected by the phaseout policy. These include 1976 type tests. These are LDTs with the following characteristics which provide the greatest risk mitigation among the characteristics that were commonly associated with those LDTs offered in 1976-- LDTs that use manual techniques without automation and are performed by lab personnel with specialized expertise, LDTs that use components legally marketed for clinical use and are designed, manufactured, and used within a single CLIA-certified lab that meets the requirements under CLIA for high-complexity testing.

The next category are HLA tests. These are for transplantation used in histocompatibility labs and meet the requirements under CLIA 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. These tests are unique in that they are generally developed and the testing is generally performed in urgent, lifesaving situations for the patient.

The next category are forensic tests that are intended solely for law enforcement purposes. These tests are subject to protections and requirements associated with the judicial process.

And finally, we have public health surveillance tests that are intended solely for use on systematically collected samples for analysis and interpretation of health data in connection with disease prevention and control and where test results are not reported to patients or their health care providers.

Now, the entire proposal is open for comment. I'd like to point out that in the notice of proposed rulemaking and in the PRIA, we have noted several areas where we are specifically seeking comment from stakeholders. These include whether specific enforcement discretion policies would be appropriate for IVDs offered as LDTs for public health scenarios beyond immediate response to emerging outbreaks.

We're seeking comment on IVDs offered as LDTs by academic medical centers-- specifically, what are the characteristics of AMC labs? And do they in fact distinguish them from other labs? Should FDA continue enforcement discretion for any requirements for tests made by AMC labs? If so, are there any additional considerations that should be taken into account? What would be the public health rationale and evidence to support a different approach for academic medical centers? For IVDs offered as LDTs by small labs, is there a public health rationale to have a longer phaseout period?

What, if any, unintended consequences may result from the proposed phaseout policy to certain patient populations, such as Medicare beneficiaries or rural populations, among others? Is there a public health rationale for continuing enforcement discretion with respect to premarket review and some or all Quality System requirements for LDTs that are being offered as of the date of issuance of this proposed rule and that are not changed with respect to indications for use or performance after that date?

Should FDA continue enforcement discretion for any requirements where outside programs can be leveraged? What should the scope of such a policy be? What characteristics of and activities within such programs justify such an approach? We look forward to stakeholder feedback on these questions, as well as any aspect of the proposed rule and phaseout policy. We encourage commenters to include the rationale behind their answers.

Here we would like to flag for awareness that the docket includes documents in addition to the notice of proposed rulemaking. These include the preliminary regulatory impact analysis, a redacted memo of examples of IVDs offered as LDTs that raise public health concerns, and a memo summarizing findings from analysis of the first 125 EUA requests from labs for molecular COVID tests. For your convenience, the links to each of these documents are provided in this table. And at the bottom of this table, you will find the direct link to the e-Comment portal.

Please submit your comments by December 4, 2023.

To recap, we are concerned that patients could initiate unnecessary treatment or delay or forgo proper treatment altogether based on inaccurate test results. This could result in harm, including worsening illness or death. The proposed rule we are discussing today is aimed at helping to ensure the safety and effectiveness of LDTs. It seeks to amend FDA's regulations to make explicit that IVDs are devices under the Federal Food, Drug, and Cosmetic Act, including when the manufacturer of the IVD is a laboratory. Along with this amendment, we are proposing a policy under which we intend to provide greater oversight of LDTs through a phaseout of our general enforcement discretion approach to LDTs.

We believe this rulemaking would also advance responsible innovation by both laboratory and non-laboratory manufacturers alike. It would better assure the safety and effectiveness of IVDs offered as LDTs and remove a disincentive for non-lab manufacturers to develop novel tests. Our economic analysis shows that the benefits would generally outweigh the costs of the proposed rule. At the end of the day, it is our belief that all patients deserve to have access to safe and effective tests, regardless of where those tests are made. This proposed rule is an important step to help ensure that health care decisions are made based on test results patients can trust.

CDR Kim Piermatteo: Thank you, Elizabeth, for your presentation. At this time, we will now transition to addressing your previously emailed questions. I'll display a group of related questions on a slide. Then I'll read each question. And Elizabeth will provide a response to each. Then we'll display the next group of related questions. I'll read them aloud individually. Elizabeth will provide a response, and so on.

As a reminder, we will not be taking live questions today. Therefore, please refrain from raising your hand in Zoom.

So Elizabeth, our first question, or actually our first topic of questions, are questions relating to scope. So the first question is, does this proposed rule apply to screening tests?

Elizabeth Hillebrenner: Hi, Kim. Yes, according to 21 CFR 809.3(a), which defines an IVD product as reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.

So this definition includes tests that provide information for screening, measuring, detecting, predicting, prognosing, analyzing, or monitoring a disease or condition, including for use in making a determination of an individual's state of health. The proposed rule does not include a proposal to remove screening tests from that definition. Moreover, the proposed rule does not propose to exclude screening tests from the phaseout policy.

CDR Kim Piermatteo: Thanks, Elizabeth. Alright, our second question is, how will the proposed rule apply to companies offering bioinformatics or other software utilized by laboratories offering LDTs?

Elizabeth Hillebrenner: Well, bioinformatics and other software that meet the definition of a device must comply with applicable device requirements. FDA has not applied its general enforcement discretion approach to non-lab manufacturers who offer their devices, such as test kits or software, that meet the definition of a device to labs. Therefore, the proposed phaseout policy and the proposed rulemaking would not apply to them. FDA's normal enforcement policies would continue to apply to such manufacturers and products.

CDR Kim Piermatteo: Thanks again, Elizabeth. Moving on to question number three, in the proposed rule, there are several categories for which FDA proposes to continue the general enforcement discretion approach, such as 1976 type LDTs. What are some examples of tests that would fall under that category?

Elizabeth Hillebrenner: Thanks, Kim. So in the NPRM, we explained that 1976 type LDTs have the following characteristics common among those tests offered in '76-- use of manual techniques without automation performed by lab personnel with specialized expertise, use of components legally marketed for clinical use in design, manufacture, and use within a single CLIA-certified lab that meets the requirements under CLIA for high-complexity testing.

So some examples of tests that might be considered 1976 type tests when they are done manually and without automation or software include various stains for cytology, hematology, and bacterial infections, cystic fibrosis sweat tests, certain colorimetric newborn screening tests, and certain tests that are based on immunohistochemistry or karyotyping or FISH. Back to you, Kim.

CDR Kim Piermatteo: Thanks, Elizabeth. OK, now we're going to move down to question four. It's a little bit of a lengthy one. So the question is, if an unauthorized LDT is used in a clinical trial, would it be considered investigational? What are the implications of the proposed rule on clinical studies of other medical products, particularly in terms of study risk determination and investigational device exemption or IDE requirements? Would FDA consider tests, such as those used to evaluate pharmacodynamics, measures-- or measure for development of drug antibodies, or monitor for safety biomarkers subject to IVD regulations when used in drug clinical development?

Elizabeth Hillebrenner: OK, an investigational device, including an investigational LDT, is a device that is the object of a clinical investigation or research involving one or more subjects to determine the safety and effectiveness of the device. This includes LDTs used for making treatment decisions about drugs or other medical products. FDA has generally expected compliance with investigational use requirements for LDTs. However, in recognition that there has been some confusion about our enforcement approach in this area, we have included compliance with investigational use requirements in Stage 4 of the proposed phaseout policy.

CDR Kim Piermatteo: Thanks, Elizabeth. Alright, that wraps up our questions related to scope. Our next group of questions is going to be related to manufacturers. So the first question-- or sorry-- number question five is, could you please explain what a manufacturer is?

Elizabeth Hillebrenner: Sure thing. So in the proposed rule, we use "manufacture" and related terms as a shorthand for the various activities that constitute manufacturing as described in FDA regulations. These include design, preparation, propagation, assembly, and processing, for example.

CDR Kim Piermatteo: Thanks, Elizabeth. Alright, number six-- the question is, what is the difference between a laboratory manufacturer and a non-laboratory manufacturer?

Elizabeth Hillebrenner: Sure. As outlined in the NPRM, we intend to phaseout our general enforcement discretion approach for LDTs so that IVDs manufactured by a lab would generally fall under the same enforcement approach as IVDs manufactured by non-labs. We anticipate that applying the same approach to these IVDs would better assure the safety and effectiveness of LDTs. We know that there is not a definition of laboratory in the Food, Drug, and Cosmetic Act, FDA regulations, or in the proposed rule.

CDR Kim Piermatteo: Thanks again, Elizabeth. So our next question is number seven. What does it mean to be manufactured and offered as an LDT?

Elizabeth Hillebrenner: We have generally considered the term lab developed test, or LDT, to mean an IVD that is intended for clinical use and that is designed, manufactured, and used within a single CLIA-certified lab that meets the regulatory requirements under CLIA to perform high-complexity testing. But we recognize that not all labs have understood the limited nature of FDA's general enforcement discretion approach. And some have been offering IVDs based on that approach even when they do not fit what the FDA generally considers to be an LDT.

So we are proposing to apply the phaseout policy 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, even if those IVDs do not fall within our traditional understanding of an LDT because maybe they are not designed, manufactured, and used within a single lab. So throughout the proposed rule, these IVDs are referred to as IVDs offered as LDTs.

CDR Kim Piermatteo: Thank you for that clarification, Elizabeth. The next question, number eight, is can research use only, or RUO, kits, reagents, or instruments manufactured outside the laboratory be used by labs?

Elizabeth Hillebrenner: So RUO components and kits can be incorporated into an IVD where the manufacturer ensures the test is in compliance with applicable requirements. So as the proposed phaseout policy would apply to all IVDs offered as LDTs, except as noted in the proposed rule, IVDs with components or kits that were previously labeled as RUO would be treated the same as tests manufactured by conventional manufacturers where the manufacturer is responsible for overall compliance, including incorporating into their Quality System any components previously labeled as RUO.

CDR Kim Piermatteo: Thanks, again. Moving down to question number nine, which is, how will the proposed rule affect modified FDA approved assays, particularly on intended use and approved sample types?

Elizabeth Hillebrenner: The proposed rule is not proposing to change the legal requirements that apply to modifications of FDA approved IVDs. If a lab modifies an FDA approved IVD, such that the laboratory is manufacturing an IVD, the laboratory and IVD must be in compliance with applicable requirements in the Food, Drug, and Cosmetic Act and FDA regulations. Under regulations, a manufacturer includes a remanufacturer, which is a person who does any act to a finished device that significantly changes the device's performance or safety specifications or intended use. The reference for that is 21 CFR 820.3(o) and (w).

A clinical laboratory that modifies an existing IVD that did not develop itself in a way that significantly changes device performance or safety specifications or intended use is considered to be a device remanufacturer. And the modified IVD is subject to applicable device requirements. For such modified IVDs, FDA would expect compliance as outlined in the phaseout policy if finalized.

CDR Kim Piermatteo: Thanks, Elizabeth. So that wraps up our questions related to manufacturers. Our next group of questions are going to be related to the phaseout of the enforcement discretion. So question number 10 is, the draft rule includes five stages to end the general enforcement discretion. Please clarify the time frame and whether the stages run concurrently or consequently-- or consequentially-- sorry. [INAUDIBLE]

Elizabeth Hillebrenner: Consecutively.

CDR Kim Piermatteo: Consecutively. [LAUGHS] Thank you.

Elizabeth Hillebrenner: No problem. So the proposal is that the general enforcement discretion approach for LDTs would be phased out over four years after FDA publishes a final phaseout policy. So the timing for each stage is based on the date FDA publishes a final phaseout policy and not based on when the previous stage ends.

To illustrate this, if, theoretically, the final rule were to be issued today, October 31, 2023, then Stage 1 where the general enforcement discretion approach for MDR requirements and correction and removal reporting requirements would end around October 31, 2024, one year from today. Stage 2, the general enforcement discretion approach for requirements other than MDR-- correction and removal reporting, QS, premarket review requirements, such as R&L, investigational use requirements, et cetera, would end around October 31, 2025. Stage 3, the general enforcement discretion approach for QS requirements would end around October 31, 2026. Stage 4, the general enforcement discretion

approach for premarket review requirements for high-risk IVDs would end around April 30, 2027. And Stage 5, the general enforcement discretion approach for premarket review requirements for moderate and low risk IVDs would end around October 31, 2027.

CDR Kim Piermatteo: Great. Thank you for that, Elizabeth. Question number 11 is, will laboratories be subject to inspections from the FDA?

Elizabeth Hillebrenner: Laboratories that manufacture IVDs are subject to inspection under Section 704 of the Food, Drug, and Cosmetic Act.

CDR Kim Piermatteo: Great. Thank you. Question number 12-- where FDA would not intend to enforce against IVDs offered as LDTs after a PMA has been submitted, within the three-and-a-half-year timeframe, until FDA completes its review of the application. Would this apply to modular PMA submissions and submission of the first PMA module or only after completing the PMA filing?

Elizabeth Hillebrenner: So under FDA's proposed phaseout policy, FDA generally would not intend to enforce against IVDs offered as LDTs after a PMA has been submitted, within the three-and-a-half-year timeframe, which includes all Modular if a manufacturer is pursuing the Modular PMA approach.

CDR Kim Piermatteo: Great. Thanks for that clarification. Question number 13-- what are the requirements for LDTs introduced between the effective date of the final rule and the time in which enforcement discretion will be phased out?

Elizabeth Hillebrenner: The proposed rule does not include a separate policy for LDTs introduced between the effective date of the final rule and the time in which the general enforcement discretion approach would be phased out. So such tests would be expected to comply with legal requirements at the time frames outlined in the phaseout policy.

CDR Kim Piermatteo: OK, thanks Elizabeth. That wraps up our questions related to the phaseout of enforcement discretion. We are now going to move to our next topic of questions, which is related to resources. Question number 14 is, how will FDA manage such an influx of submissions from laboratories?

Elizabeth Hillebrenner: So under FDA's proposed policy, FDA generally would not intend to enforce premarket review requirements against IVDs offered as LDTs after a PMA, 510(k) or De Novo request has been submitted within the appropriate timeframe until FDA completes its review. We proposed a phaseout timeline for which premarket review expectations coincide with MDUFA VI. Thus, the level of user fee resources and an associated fee structure could be discussed in MDUFA VI negotiations.

We're also looking at ways to reduce our resource needs. For example, FDA is currently working to enhance our Third-Party Review Program, which was reauthorized under MDUFA V. And we think it could be used extensively for LDTs.

One alternative in FDA's preliminary regulatory impact analysis contemplates that at least half of new LDTs subject to 510(k) requirements could come through that program. We're already aware of certain CLIA-accredited organizations that may be interested in serving in this third-party review role. And to

the extent they already perform audits for the CLIA program, labs may be familiar with them and inclined to use the Third-Party Review Program.

We're also seeking comment on leveraging existing programs, such as those of the New York State Department of Health or the Veterans Health Administration. And we've posed several questions in the NPRM, the resolution of which could impact the resources necessary to support the final rule.

CDR Kim Piermatteo: Thanks, Elizabeth. Moving on to question number 15-- when will laboratories be required to pay user fees during the phased in process?

Elizabeth Hillebrenner: There are user fees associated with registration and listing-- Stage 2, I believe. And premarket review, Stages 4 and 5.

CDR Kim Piermatteo: Great. Question 16-- what will be the user fees associated with LDT-related product submissions?

Elizabeth Hillebrenner: The current user fee program ends on September 30, 2027, at which time Congress may reauthorize a new iteration of the program based on a negotiation between FDA and regulated industry. As a result, we can't estimate at this time what those negotiated figures will be in the future.

CDR Kim Piermatteo: Thank you. Question number 17-- will there be a small business designation for laboratories for reduced submission fees?

Elizabeth Hillebrenner: I can tell you the current user fee program does include special considerations for small businesses.

CDR Kim Piermatteo: Thanks Elizabeth. So that now wraps up our questions related to resources. Our next group of questions is related to CLIA. And question number 18 is, how does the rulemaking proposal intersect with the CLIA program?

Elizabeth Hillebrenner: So FDA regulates devices, including IVDs, under the statutory authorities of the Food, Drug, and Cosmetic Act, which is distinct from the Public Health Services Act under which CLIA falls. The CLIA program is focused on laboratory operations, while the FDA's device program is focused on the IVDs themselves and other devices. As described in a fact sheet on CMS's website the two frameworks are different in focus, scope, and purpose. But they are intended to be complementary.

The proposed policy in the NPRM leverages CLIA where appropriate. Specifically, we propose to enforce a subset, rather than all QS or Quality System requirements for labs when all manufacturing activities occur within a single CLIA-certified lab that meets the regulatory requirements to perform high-complexity testing and where the IVD is not distributed outside of that lab.

CDR Kim Piermatteo: Thanks, Elizabeth. Our next question, question number 19, is, will CLIA certification still be necessary?

Elizabeth Hillebrenner: So the proposed rulemaking would not change requirements for laboratory certification under CLIA.

CDR Kim Piermatteo: Great. Alright, our next group of questions is going to be related to implementation. The first question in this group is question number 20. And the question is, what accelerated or streamlined submission process will be available for LDT class III medical device approval?

Elizabeth Hillebrenner: So FDA estimates that only about 5% of LDTs would undergo review through the premarket approval pathway. We expect that most LDTs subject to premarket review requirements would be eligible for either the 510(k) or De Novo pathways.

Additionally, we have a Breakthrough Devices Program that is a voluntary program for certain medical devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions and for which the device represents a breakthrough technology, no cleared or approved alternative exists, and the device offers significant advantages over existing cleared or approved alternatives or the device's ability-- excuse me-- the device's availability is in the best interest of patients.

So this Breakthrough Devices Program is intended to speed up development, assessment, and review while preserving the statutory standards for premarket approval, 510(k) clearance, and De Novo marketing authorization. The program does this by offering manufacturers an opportunity to interact with FDA expert to efficiently address topics as they arise during the development and premarket review phase. This interaction can help manufacturers receive feedback from the FDA and identify areas of agreement in a timely way.

Manufacturers of devices in the Breakthrough Devices Program can also expect prioritized review of their submission. Recently, just last month on September 14, 2023, we issued updates to the final guidance on breakthrough devices. And on Tuesday, November 14, we will host another webinar for the medical device industry and other stakeholders to discuss this updated final guidance.

CDR Kim Piermatteo: Thanks, Elizabeth. So our next question, question number 21, is, will FDA expect clinical validity of each LDT to be established “from scratch” even when evidence is available in the literature?

Elizabeth Hillebrenner: So FDA considers the least burdensome approach when evaluating premarket submissions for devices that is consistent with applicable requirements. Therefore, provided available literature is adequate to demonstrate the test is clinically valid. FDA would not expect labs to generate additional clinical validity data. It is our current practice in review of IVDs to leverage information from the literature when it is available and applicable. Further, we've also established a recognition program for databases of human genetic variants that provides a mechanism for test manufacturers to leverage information and FDA recognized databases to support clinical validity of their tests.

CDR Kim Piermatteo: Thanks, Elizabeth. Now we're going to move on to question number 22. And that question is, how would FDA regulate tests that change over time, such as next generation sequencing? Does FDA support the use of Predetermined Change Control Plans or PCPs as related to LDTs?

Elizabeth Hillebrenner: Yes, absolutely, FDA is open to the use of Predetermined Change Control Plans for LDTs and has actually seen them used already in that context. If a PCCP has been cleared or approved by FDA for the test, then the manufacturer can make changes to the test according to the

cleared or approved PCCP without additional submission to FDA. Now, if there is no cleared or approved PCCP for the test, certain changes would be subject to premarket review requirements. For example, changes to a cleared test that could significantly affect safety or effectiveness would be subject to premarket review requirements.

CDR Kim Piermatteo: Thanks again. We will now move on to question number 23. That question is, how would device design controls be applied to existing LDTs that were developed prior to the application of such design controls through this rulemaking process, in reasonable reliance upon a different regulatory framework under which they were not then required?

Elizabeth Hillebrenner: IVDs, including LDTs, are devices and therefore are subject to applicable device requirements under the Food, Drug, and Cosmetic Act and FDA regulations, even though FDA has generally exercised enforcement discretion for most LDTs. However, as discussed in the NPRM, FDA intends to phaseout its general enforcement discretion approach for LDTs. So if you wish to comment on how design controls should be enforced for marketed LDTs, we encourage you to submit a comment to the docket. For example, comments may address whether for currently marketed LDTs FDA should focus its enforcement of design controls on modifications to those marketed LDTs.

I just want to add, too, Kim, that we recognize that this is an area where more guidance from FDA may be helpful for labs. So we anticipate having more resources for labs to aid in these types of implementation inquiries.

CDR Kim Piermatteo: Great. Thanks for providing that additional note, Elizabeth. Our next question then, moving down to question number 24, is, many LDTs do not have package inserts such as those found in many IVD kits. How does FDA see the implementation of FDA labeling requirements for LDTs?

Elizabeth Hillebrenner: So I would refer folks to 21 CFR 809.10 which sets forth specific labeling requirements for IVDs, including specific information that must be included. Labs may comment on how they can meet these requirements, including how the information might be encompassed in more than one document, such as maybe the test protocol, test report template, or a test menu. And then FDA intends to consider providing more targeted guidance and/or making additional resources available on specific topics, such as compliance with applicable labeling requirements over the course of the phaseout period.

CDR Kim Piermatteo: Thank you, Elizabeth. OK, then our next question is question number 25. And that question is, does the FDA plan to provide support to the laboratories to come into compliance with the new requirements?

Elizabeth Hillebrenner: Absolutely. As I have mentioned, we appreciate the need for education and other support for labs to come into compliance. FDA's requirements are not new. But we understand that many labs may not be familiar with them.

During the COVID pandemic, we learned new ways to engage and interact with stakeholders, such as town halls and frequently asked questions. We plan to leverage what we learned and build on it going forward. We also recognize that additional guidance documents may be needed, such as guidance on appropriate validation, particularly with respect to clinical validity.

All guidance documents will be developed according to good guidance practices with an opportunity for comment as appropriate. And as mentioned in the NPRM, we intend to consider making additional resources available on specific topics, such as compliance with applicable labeling requirements, over the course of the phaseout period. We welcome feedback to the docket about areas in which labs might need more assistance so that we can focus these efforts accordingly.

CDR Kim Piermatteo: Great. Thanks, Elizabeth. We will now move to our last previously submitted question for today. And that question is number 26. And it states, does the FDA intend to extend the comment period per request to the docket?

Elizabeth Hillebrenner: After considering the request to the docket and other factors, including the extensive background of public comment on this topic and the public health benefits of proceeding expeditiously, FDA has determined to proceed with the standard 60-day comment period. As stated in the notice of proposed rulemaking, comments on the proposed rule must be submitted to the docket by December 4, 2023, in accordance with the procedures described in the notice.

CDR Kim Piermatteo: Great. Thank you for clarifying that, Elizabeth. Alright, again, I really want to thank Elizabeth for her presentation and for providing all of the responses to your previously emailed questions. That wraps up our previously submitted questions and our webinar for today. I'd like to turn it back over to Elizabeth for her final remarks on today's topic. Elizabeth.

Elizabeth Hillebrenner: Thanks, Kim. And I just wanted to thank everyone for joining us this Halloween afternoon. We hope the webinar has been helpful. And we look forward to receiving your feedback in the docket by December 4. Thank you.

CDR Kim Piermatteo: Thanks again. And to wrap up for me, for your information, printable slides of today's presentation are currently available on CDRH Learn at the link provided on the slide under the section titled In Vitro Diagnostics. And a recording of today's webinar and a transcript will be posted to CDRH Learn under the same section and subsection in the next few weeks. A screenshot of where you'll be able to find these webinar materials has been provided on this slide.

If you have additional questions about today's topic, please send an email to LDTProposedRule@fda.hhs.gov. If you have general medical device inquiries, please feel free to email DICE at DICE@fda.hhs.gov.

Lastly, we hope you are able to join us for a future webinar like the one that Elizabeth mentioned earlier on breakthrough devices. That one's on November 14. But you can find a listing of all of our upcoming webinars at the link provided on the bottom of the slide at www.fda.gov/CDRHWebinar.

Thank you all again for joining us. This concludes today's CDRH webinar. Have a great day.

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