FDA's Total Product Life Cycle Approach to In Vitro Diagnostic Products (IVDs)
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Moderator: CDR Kim Piermatteo

CDR Kim Piermatteo: Hello and thanks for joining us for today's CDRH Webinar. This is CDR 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 within CDRH. I'll be your moderator for today's webinar.

We are holding today's webinar for laboratory manufacturers and other interested parties to discuss the FDA's Total Product Life Cycle, or TPLC, approach to the oversight of in vitro diagnostic products or IVDs. The FDA's TPLC approach allows the FDA to review and monitor medical devices throughout their life cycle by taking into account all available information on safety and effectiveness.

I'd now like to introduce today's presenter, Dr. Brittany Schuck, Deputy Office Director for the Office of Health Technology number seven for in vitro diagnostic devices within the Office of Product Evaluation and Quality within CDRH.

We'll begin with a presentation from Brittany and then address previously emailed questions about today's topic. Before I turn it over to Brittany, I'd like to provide two administrative 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.

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

Brittany Schuck: Thank you, Kim, for the introduction. Welcome, everyone. Thank you all for attending our webinar today on FDA's Total Product Lifecycle Approach to in vitro diagnostic devices, or IVDs. Our objectives for this webinar include describe FDA's total product life cycle approach and FDA's roles and responsibilities in regulating in vitro diagnostic devices throughout the lifecycle of these products and describe the organizational units within FDA that are responsible for regulating IVDs.

There are two Centers within FDA that are responsible for helping to assure that IVDs are safe and effective: the Center for Devices and Radiological Health, known as CDRH, and the Center for Biologics Evaluation and Research, known as CBER. We are going to focus on CDRH first.

CDRH assures that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products. We provide consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee. We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S. Our most critical resource to achieve this mission is our staff, some of whom we'll introduce today.

We recognize that many IVD manufacturers, including laboratories, are driven by similar public health missions when developing new or improved IVDs. We enjoy working with IVD manufacturers, including

laboratories, to ensure that patients and healthcare providers have safe and effective IVDs they can rely on to make important patient care decisions.

Many regulatory activities relating to IVDs are overseen by the Office of Health Technology seven, Office of In Vitro Diagnostics. Our office sits within the Office of Product Evaluation and Quality or OPEQ within CDRH. There are four review divisions and one operational division within the Office of In Vitro Diagnostics. Each review division shares a similar organizational structure but has different subject matter expertise. Each division has a team of personnel who are responsible for the TPLC oversight of devices in their area. These teams include scientists and medical officers with expertise in review of safety and effectiveness, including many who have worked in clinical laboratories. The Office of In Vitro Diagnostics, like other parts of FDA, is comprised of physicians, statisticians, engineers, biologists, chemists, geneticists, and others, who evaluate the science behind medical devices to ensure they are safe and effective for use.

Courtney Lias directs the Office of IVDs. I am a Deputy Director, along with my colleagues Toby Lowe and Ryan Lubert. Sara Brenner is the Chief Medical Officer and Associate Director for Medical Affairs. The Office of In Vitro Diagnostics serves as the primary source for scientific and medical expertise within CDRH with regard to the safety and effectiveness of IVDs. We oversee IVDs across the TPLC, engaging with device manufacturers pre and postmarket.

As we'll discuss throughout this presentation, we review Investigational Device Exemptions, premarket submissions, and adverse event reports, among other things. We also provide initial support for questions related to regulatory programs in response to requests from medical device and health technology industries, trade associations, and other Federal agencies, other countries, State agencies, and the general public. We advise, coordinate, and provide consultation to Agency officials on office programs and policies concerning premarket review, compliance, and quality, and postmarket surveillance activities. We also participate in the development of national and international consensus standards, and voluntary guidelines through interaction with national and international standards committees.

The Division of Chemistry and Toxicology Devices, led by Director Marianela Perez-Torres and Deputy Director Paula Caposino, is responsible for oversight of chemistry and toxicology in vitro diagnostic devices. For example, hormone tests, creatine phosphokinase tests, glucose meters, and drug monitoring tests.

The Division of Immunology and Hematology, led by Director Lea Carrington and Deputy Director Takeesha Taylor-Bell, is responsible for oversight of immunology and hematology in vitro diagnostics devices. For example, immunoglobulin tests and prothrombin time tests.

The Division of Microbiology Devices, led by Director Uwe Scherf and Deputy Directors Joe Briggs and Noel Gerald, is responsible for oversight of microbial in vitro diagnostics devices, including viral respiratory, human papilloma virus, general viral, hepatitis, general bacteria, antimicrobial susceptibility, bacterial respiratory and medical countermeasures diagnostic devices.

The Division of Molecular Genetics and Pathology, led by Acting Director Soma Ghosh, is responsible for oversight of molecular genetics and pathology in vitro diagnostic devices. For example, liquid biopsy cancer tests, cancer predisposition risk assessments, and oncology companion diagnostics.

The Division of Program Operations and Management, led by Director Amy Zale, is responsible for supporting the other divisions and office specific programs.

Within a given product area, CDRH teams are responsible for overseeing regulatory requirements across the TPLC. Combining oversight of premarket and postmarket activities together in the same team within CDRH helps ensure that our staff have a full picture of the device, allowing us to leverage knowledge of premarket data to inform our postmarket oversight and compliance decisions, and vice versa, leveraging postmarket knowledge to make better informed premarket decisions. Ultimately, this helps FDA respond to safety issues in a timely manner. In addition, this approach helps FDA build strong and interactive relationships with device manufacturers so that challenges may be solved more efficiently, and FDA can support agile innovation of novel IVDs.

Some types of IVDs are regulated by the Center for Biologics Evaluation and Research or CBER, which is a separate center in FDA from CDRH. CBER's mission is to ensure the safety, purity, potency, and effectiveness of biological products including vaccines, allergenics, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. CBER and CDRH staff work together to maintain consistent approaches to oversight of IVDs.

CBER's Office of Blood Research and Review or OBRR regulates some of these IVDs. The Division of Emerging Transfusion-Transmitted Diseases, led by Director Dr. Hira Nakhasi and Deputy Director Dr. Peyton Hobson, is responsible for regulating donor screening tests for infectious diseases and diagnostic and supplemental tests for retroviruses. For example, blood donor screening tests for HIV, HBV, HCV, West Nile virus, Chagas disease, malaria and babesia, and HIV diagnostic, supplemental and viral load assays.

The Division of Blood Components and Devices, led by Acting Director Dr. Orieji Illoh and Deputy Director, Dr. Wendy Paul, is responsible for regulating tests intended to determine donor and recipient compatibility in transfusion and transplantation. For example, immunohematology tests, molecular red blood cell antigen tests, and human leukocyte antigen or HLA tests. Inquiries related to IVDs regulated in OBRR should be directed to Cherry Geronimo, Director of the Regulatory Project Manager Staff.

Finally, the Office of Cellular Therapy and Human Tissue within CBER's Office of Therapeutic Products or OTP is responsible for oversight of some IVDs associated with tissue and/or organ transplant. For example, histocompatibility tests and devices for enumeration of certain cells. Inquiries regarding IVDs regulated in OTP should be directed to the email OTPRPMS@fda.hhs.gov.

Now that we have covered who we are, let's dig into what we do. FDA maintains oversight over the total product lifecycle of an IVD and interacts with manufacturers throughout the lifecycle of the device. As you will see here, the Quality System, or QS, requirements apply across the entire lifecycle, starting with the design. In cases where validation includes a clinical study, investigational requirements may apply. Generally, for moderate and high risk IVDs, premarket review requirements apply. This generally includes review of the analytical and clinical validation as well as safety information. Upon launching the test for clinical use, registration and listing requirements as well as labeling requirements apply and must be met. Registration and Listing must be updated throughout the clinical use of the device. Labeling requirements must continue to be met and manufacturers are required to report certain

adverse events, corrections, and removals to FDA. We portray this as a continuous cycle as we often see experience in clinical use inform iterative device design, particularly in the IVD space.

Quality System Requirements apply across all phases of the lifecycle. Manufacturers are required to establish and follow quality systems to help ensure the safety and effectiveness of their devices on an ongoing basis. If quality system requirements are only considered as a postmarket factor, after device launch, design issues may be missed. Historically, we have seen that a significant portion of device recalls were attributed to faulty design and may have been prevented by adequate design controls. Stay tuned for more information about Quality Systems in a future webinar.

In the design phase of an IVD, a manufacturer typically considers how to address a need observed by their customers, which may be laboratories that would use such a test, healthcare providers who would order the test, and patients for whom the test is used. The test is then designed to meet the needs of the users, both patients and healthcare providers, in accordance with the manufacturer's business practices. Much of the design and development phase may be conducted by the manufacturer without interaction with FDA. For most IVDs, FDA requires use of design controls to ensure manufacturers approach device design and modifications systemically, ensuring that the original design and any changes have been properly evaluated and do not have unintended consequences.

It is critically important that device performance is robustly validated to ensure that IVDs are safe and effective for their intended use. Simply put, the validation should show that the device does what it is designed and intended to do. So once a device is finalized, but before being used clinically, the manufacturer is responsible for designing and conducting studies to demonstrate device performance. This typically includes analytical validation studies, and, in some cases, clinical validation studies. Depending on the device, additional studies may also be needed, such as usability studies.

The validation phase is often where the most interaction with FDA occurs, and we will spend most of our time today focused on this phase. We'll discuss the general types of validation typically needed, the types and steps of premarket review, where applicable, and resources to help you understand FDA's current thinking.

First, let's talk about the primary types of validation. All tests should be appropriately validated prior to use, whether or not they require FDA premarket review. For IVDs that do require FDA premarket review, a significant portion of the information typically provided in a premarket submission is the information to support the analytical and clinical validity of the IVD.

Analytical validation data is the information that demonstrates that an IVD accurately and reliably measures or detects the analyte or analytes of interest. Analytical validation studies often include an assessment of measurement imprecision, identifying interfering substances and assessing analytical measurement bias. The specific information necessary to support the analytical validity of an IVD often depends on the analyte detected, the technology used to measure it, as well as the specific claims made by the manufacturer. In addition, the type and magnitude of the risks posed to patients when they are treated based on an undetected wrong result is an important consideration.

Clinical validation assesses the accuracy and reliability with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient. As discussed on our last slide regarding analytical validation, the type of clinical validation information that is necessary

can vary significantly depending on the test system. For some analytes, such as serum glucose, where the clinical validity of the analyte has been documented previously and is broadly accepted by the clinical community, the clinical validity data typically demonstrates that the test measures the analyte as well as other FDA authorized tests, for example through a method comparison study. In other cases, clinical validity data from a clinical study is submitted, such as when the new test does not align well to other available test systems or there is no available comparator to measure the same analyte. In these scenarios, a clinical study typically demonstrates how well the test performs to provide information on the clinical condition or predisposition for which it is intended to be used.

Some validation studies may be clinical investigations. For the subset of studies where the use of the investigational IVD in the study poses a significant risk to patients, the sponsor would need to submit an Investigational Device Exemption application to FDA and receive FDA approval before beginning the study. We are planning to have a webinar in 2025 with more information on this topic.

Once the device is fully validated, that is typically the time a manufacturer would submit a premarket submission to FDA, if one is required, so let's look at the different premarket pathways and which require submissions to FDA.

As discussed in FDA's IVD classification webinar on our website, which you can reach through referenced link on this slide, FDA has a risk-based approach to device regulation, including device classification. Although there are exceptions, the classification of a device generally correlates with its risk category. Most Class I devices are low risk, most Class II devices are moderate risk, and most Class III devices are high risk. The classification then drives the type of premarket submission that will be needed for the IVD.

The IVD classification webinar has more detailed information on classification and the different types of premarket submissions. Generally, most Class 3 devices are reviewed through the Premarket Approval Application, or PMA, process. Most Class 2 devices, are reviewed through the 510(k) process, also referred to as 510(k) Notification. The De Novo classification pathway is used for certain novel devices, meaning the type of device has not been classified or previously approved through the PMA pathway, that are moderate or low risk. Finally, most Class 1 devices, and some Class 2 devices, are exempt from premarket review, and do not require a premarket submission. This is often referred to as 510(k) exempt or exempt from Premarket Notification.

Some Class 2 devices have Special Controls which are specific regulatory requirements that apply to specific Class 2 devices. Special controls are generally specific to a particular device type and can be found under the regulation for the device type. Special controls are often established for a new device type at the time that a De Novo authorization is granted. Special controls can include, for example, performance standards, special labeling requirements, or analytical and clinical validation requirements.

The Medical Device User Fee Amendments, also called MDUFA, authorizes the FDA to collect user fees for the process for the review of medical devices. The user fee program is negotiated with regulated industry every five years. At the end of these negotiations, FDA commits to specific performance goals and program enhancements and industry commits to providing resources through user fees to support them. This includes goals for FDA to perform our reviews in a specific period of time, with the length of time varying based on the type of submission.

During the current MDUFA V program, FDA aims to complete review of a 510(k) submission within 90 days. For a De Novo submission, FDA aims to complete its review within 150 days. And for PMAs, the goal review time is 180 days. If a file is placed on hold, where the FDA has requested additional information from the manufacturer, the time the file is on hold does not count toward the FDA review time, though it does count towards the FDA and industry's shared outcome goals, referred to as total time to decision.

The current user fee agreement, referred to as MDUFA V, since it is the fifth iteration of the Medical Device User Fee Amendments, expires on September 30, 2027. This is before FDA expects compliance with premarket review requirements for IVDs offered as LDTs under the phaseout policy described in the preamble to the LDT Final Rule. We expect that MDUFA VI will be negotiated and authorized before that time. More information on user fee agreements can be found on FDA's website linked on this slide.

The regulatory requirements for CBER regulated devices are very similar to those already described; however, there are a few differences. In addition to the types of premarket submissions already described on our earlier slide, certain CBER regulated devices are submitted through Biologics License Applications or BLAs, which are under section 351 of the Public Health Service Act or PHS Act. For example, IVDs to test blood donations for transfusion-transmitted infections, such as HCV and HBV, are reviewed through BLAs.

Similar to the previously discussed types of premarket submissions, based on user fee agreements, FDA has also agreed to generally perform review of BLAs in a specific time period. For standard original BLAs, FDA aims to complete review within 10 calendar months of the 60-day filing date. And for priority original BLAs, the goal review time is within six calendar months of the 60-day filing date.

We noted that some devices are exempt from premarket review. The preamble to the LDT final rule includes several targeted enforcement discretion policies. It is important to note that there is a difference between enforcement discretion and an exemption. Under an Enforcement Discretion policy, FDA states its general intention to not enforce compliance with certain requirements such as, but not limited to, Premarket Notification, even though those requirements do apply to that device. Regardless of any Enforcement Discretion policy, FDA retains discretion to pursue enforcement action at any time against violative IVDs when appropriate.

On the other hand, exemption from Premarket Notification is when all devices of a specific type are exempt from the requirements of Premarket Notification, which is stated in the classification regulation for that device type. Exemption means those requirements do not apply to that type of device, subject to certain limitations. However, even if a device is exempt from Premarket Notification, other applicable FDA requirements, such as Quality System requirements and adverse event reporting, generally still apply.

Now that we have discussed the different premarket pathways, we'll focus on the devices that do require premarket review submission and FDA review.

FDA generally reviews information supporting analytical validity, clinical validity, and safety. As discussed, there are different types of premarket submissions, depending on the risk of the device. Most IVDs are Class II, moderate risk, and are reviewed through the Premarket Notification or 510(k) pathway. In a 510(k) submission, FDA generally reviews information supporting analytical validity, clinical validity,

and safety, along with other information regarding the device, to determine if the device is substantially equivalent or SE to a legally marketed device of the same type, referred to as a predicate device.

In Premarket Approval Applications or PMAs, FDA generally reviews information supporting analytical validity, clinical validity, and safety, as well as manufacturing information, to ensure a reasonable assurance of safety and effectiveness prior to marketing.

For De Novo Classification Requests, or De Novos, FDA generally reviews information supporting analytical validity, clinical validity, and safety, along with other information, and determines the level of regulatory control needed to provide reasonable assurance of safety and effectiveness. If the De Novo request is granted, this action establishes a new device type that will be the subject of a new classification regulation as well as special controls, if any. Such devices can then serve as a predicate device for future 510(k) submissions for devices of the same type. Future devices of the same type must meet the special controls established for the device type.

Before we get into what happens after submission to FDA, let's first talk about how to prepare for a submission. FDA aims to be as transparent as possible about our expectations, and there are several resources available as you design your validation studies to ensure your studies will provide the type of information that will result in a successful premarket submission to FDA.

One such resource is FDA guidance documents, which can be found at the link on this slide.

Additionally, FDA recognizes several consensus standards, including from the Clinical & Laboratory Standards Institute or CLSI, and the International Organization for Standardization or ISO, which describe procedures and considerations for specific assessments, such as interference and precision. Standards that are recognized by FDA are included in a database on our website, which also includes a link to a guidance document on the Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices. Using applicable FDA recognized consensus standards to guide your validation approach may help to ensure that the information you're providing is more likely to result in a successful premarket submission to FDA.

Another resource that can provide information on relevant device review precedents is our database of FDA Decision Summaries. For those devices which FDA has determined, through premarket review, that they meet the applicable statutory and regulatory requirements for marketing in the U.S., FDA has published summaries of the information used by FDA to make our decision. We call these Decision Summaries. These are also referred to as Summaries of Safety and Effectiveness Data or SSEDs for devices approved through the PMA pathway.

There are separate databases for each of the different submission types. The links to the four databases are provided on this slide. We'll go into more detail on FDA Decision Summaries and how to use them in the following slides. You'll see that CBER reviewed 510(k)s are in a separate database from the CDRH reviewed 510(k)s. CBER's database includes CBER Cleared 510(k) Submissions with Supporting Documents, which includes 510(k) summaries for each submission. These are slightly different from the decision summaries in the other databases, but typically contain much of the same information.

These public Decision Summaries are a great resource to get a sense of the type of information used to support a premarket submission. The summaries include a description of the device, including the type

of test and the intended use, a comparison to the predicate device for IVDs cleared through the 510(k) pathway, a list of the relevant standards and guidance documents that were used to support the submission, as well as descriptions of the analytical and, when applicable, clinical studies conducted, including the performance that was observed.

It is important to know that, even if there isn't an example of an identical IVD, reviewing publicly available information about FDA's reviews of similar IVDs, or IVDs with some of the same characteristics, may give you an idea about what general kinds of information will be expected in your submission. For example, if you are planning to validate a test in the same population or using the same technology as an authorized test, you can see what types of testing were performed to demonstrate performance for those patient populations or that technology.

Now let's look at an example of a 510(k) database entry. For this example, assume I'm interested in preparing a premarket submission for a folate assay and I'd like to see what some previous successful submissions have included. I can go into the 510(k) database and search for folate and a number of 510(k)s will show up as a result. Here I'm showing you an example of one of those 510(k)s, K172201. The database shows quite a bit of the relevant information, including the device name, the regulation it is under, and the decision made on this particular 510(k). There's also a link to the Decision Summary for this 510(k).

Clicking on the link in this blue box opens the Decision Summary for this IVD, which shows some of the relevant information provided to FDA. Here's what the beginning of the Decision Summary looks like. There are a number of descriptive items that explain the IVD and its most important characteristics. For example, the measurand, the type of test and the applicant. Below this, in other regulatory sections, you'll be able to see the intended use, which was discussed at length in the classification webinar, as well as the validation information for this test.

Here's an example of the type of validation information included in a Decision Summary. This can help you understand the type of validation information FDA may be expecting to review. Here we have a summary of a precision study from the Decision Summary for the folate 510(k) we were just looking at. The precision and reproducibility section in the Decision Summary describes how the study was done, including the samples used and the sources of variability assessed in the study, as well as the data from the study. There is also a reference to the FDA recognized CLSI guideline that was utilized in designing the precision study.

An IVD manufacturer planning to submit a 510(k) for a similar folate test system can look at this description and anticipate that if they design a similar study, with the same number and types of samples, across the same conditions with similar data, that should yield the type of information that FDA has previously found appropriate to support a Premarket Notification for a similar type of IVD.

After reviewing FDA-recognized standards and FDA Decision Summaries, you might still have questions about your validation approach and how to meet FDA's regulatory requirements. The Q-Submission program gives you an opportunity to interact with the Agency about questions you may have regarding validation or in preparing for premarket submissions. Typically, these requests are sent to FDA prior to premarket submission, although they can be submitted at any time. Questions can be on IVD validation, study design, or unique aspects of your IVD, among other topics. Manufacturers may find these interactions most helpful when they've already reviewed publicly available resources such as CLSI

guidelines and the FDA databases mentioned previously and have specific, targeted questions that are not addressed elsewhere. You may also hear these referred to as Pre-Submissions, which are one type of Q-Submission. The link to the Q-Submission guidance is provided on the slide.

Next up, we'll walk through the premarket review process once a submission is made to FDA. Once the submission is sent to FDA, the file is assigned to a lead reviewer in the division and team with expertise in that device type. For every review, the IVD manufacturer will know who their FDA lead reviewer is within a short time after FDA receives the submission, and that person will serve as the main point of contact for questions during the review.

Each review has two main phases, an administrative review phase, where FDA will screen the submission to ensure that it is administratively complete, and a substantive review phase, where the review team assesses the data in the submission. During any part of the review process, reviewers may contact the manufacturer via email or phone with questions about the information provided in the submission that the reviewer thinks can be addressed within a few days. This is called Interactive Review, and this type of informal interaction helps the review process move along quickly and efficiently.

If there are questions that will take longer than a few days to answer, or will require a new study, FDA may request additional information through a formal letter, typically sent by email, and place the review on hold until the manufacturer responds. A hold means that FDA's review clock is paused, as mentioned earlier, and the time for the manufacturer to respond does not count towards FDA's review time.

The Additional Information request, also called an AI letter or a Hold letter, includes the amount of time that manufacturers generally have to respond to the request. For both 510(k)s and De Novos, manufacturers generally have 180 days to respond to requests for additional information. For PMAs, manufacturers generally have up to 360 days to respond to requests for additional information.

Importantly, as part of the user fee agreements, FDA and manufacturers agree on shared outcome total time to decision goals for PMAs and 510(k)s, averaged across received submissions. As discussed in the MDUFA V Commitment Letter, the FDA and applicants share the responsibility for achieving the objective of reducing the average Total Time to Decision, while maintaining standards for safety and effectiveness. These goals adjust over the course of the MDUFA V performance period. For PMAs, by the end of MDUFA V, the average shared outcome total time to decision goal is 285 calendar days. For 510(k)s, by the end of MDUFA V, the average total time to decision goal is 112 calendar days.

At the end of the review, a decision letter will be sent by the FDA lead reviewer via email stating FDA's decision on the submission.

Following a successful decision on the premarket submission for a device, and provided they meet all other applicable requirements such as quality system requirements, the device manufacturer can begin to commercialize and market their device.

The device manufacturer must register their establishment, if not already registered, and list their device with FDA. There will be a webinar in December that will focus in greater detail on the Registration and Listing processes.

After the device has entered the market, registration and listing must be updated throughout the clinical use of the device. Labeling requirements must continue to be met and manufacturers are required to maintain compliance with Quality System requirements for ongoing quality manufacture of the test system, complaint handling, etc. Manufacturers are required to report certain adverse events, corrections, and removals to FDA. More information on medical device reporting, and corrections and removal reporting requirements, can be found in a webinar from earlier this year, which is linked on the slide.

FDA uses information from postmarket data, such as MDR trending analysis, to inform premarket reviews. In addition, FDA can receive complaints regarding devices and oversees corrections and removals, sometimes called recalls, for devices that are not functioning as intended.

In addition, device manufacturers may be inspected by FDA. These inspections are performed by FDA's investigators in field offices around the globe. FDA also works with device manufacturers to identify shortages and to minimize the impact of shortages on the public health system.

CDRH's Office of Supply Chain Resilience is responsible for managing CDRH's activities to anticipate and prevent disruptions to the supply chain for medical devices, including managing a medical device shortage list. This publicly available list of devices determined to be in shortage can be located at the link on this slide.

CBER's Office of Compliance and Biologics Quality is responsible for managing activities to prevent and mitigate disruptions to the supply chain for CBER-regulated medical devices. CBER's current shortages list can be found at the second link on this slide.

FDA may also issue safety communications or letters to healthcare providers to publicly share information about specific risks related to specific devices or types of devices or other issues identified through the TPLC framework that may affect public health. For example, FDA has issued two safety communications regarding cybersecurity vulnerabilities with instruments used in clinical laboratories.

As data is obtained during the clinical use and surveillance phase of a product life cycle, that information can be used by both manufacturers and by FDA to inform future device design and premarket reviews.

For example, while a device is being marketed and used clinically, a manufacturer may decide to modify the device based on information they have collected from its use. These modifications could be intended to improve performance or speed of testing, to update to a new technology or to fix a problem identified by users once the device is marketed.

Modifications are expected to be made and validated under the manufacturer's quality system. Additionally, certain modifications may require a premarket submission and, in some cases when the modification is intended to correct a problem, a report of a correction or removal, also known as a recall. We have included on the slide links to two guidance documents that may be helpful references.

In addition, information obtained after the device is marketed can be used by FDA to inform premarket reviews of new devices. For example, MDRs and recalls may identify a problem where a design change is needed. FDA reviewers may then consider these issues during the review of future premarket submissions to prevent the occurrence of similar issues in new devices. One real life example was the

identification of high levels of biotin interference affecting certain types of IVDs through surveillance activities during clinical use. FDA provided safety communications making the public aware of the potential for this interference.

In addition to those safety communications, FDA used the information to inform future premarket reviews and began requesting additional biotin interference testing in premarket submissions for tests utilizing technologies that were likely to be affected by high levels of biotin. This resulted in more accurate labeling with regards to the risks of biotin interference. Eventually manufacturers created new generations of some tests with biotin interference remediation such that the tests were no longer as vulnerable to interference from high levels of biotin.

In summary, the major points to take away from today's webinar are as follows: FDA maintains oversight over the entire total product lifecycle of an IVD, and FDA may interact with the manufacturer at various points during the life cycle of their IVD; CDRH and CBER staff have significant expertise across the TPLC of IVDs and there are many opportunities for feedback from FDA as manufacturers work to comply with applicable regulatory requirements.

This slide, along with the next two, include resources and references mentioned during today's webinar.

We have an upcoming webinar on December 3, 2024, from 1 to 2 pm eastern, and will provide additional information on the Registration and Listing process during that webinar. We hope that you will join us for the December and for future webinars. Now I will hand it back over to Kim.

CDR Kim Piermatteo: Thank you for that presentation, Brittany. We'll now transition to address some previously submitted questions related to today's topic. Joining us for this segment is Toby Lowe, Acting Deputy Director for the Office of Health Technology number seven for in vitro diagnostic devices within the Office of Product Evaluation and Quality within CDRH. Thanks for joining us Toby.

Toby Lowe: Thanks Kim. Good to be here.

CDR Kim Piermatteo: So for this segment, I'll read a question aloud and then Brittany, or sorry Toby, will provide a response. We will not be taking live questions during today's webinar, therefore, please refrain from raising your hand in Zoom.

So Toby let's get started. For our first question, the question is, does the frequency or volume a test is used impact the applicable FDA regulatory requirements?

Toby Lowe: Thanks Kim. In general, FDA regulatory requirements are not impacted by the frequency or volume a test is used. However, we note that devices that are designed to treat or diagnose a disease or condition that affects not more than 8,000 individuals in the United States on an annual basis may be eligible for a different type of premarket submission, called a Humanitarian Device Exemption. In the case of devices used for diagnostic purposes, Humanitarian Device Exemptions are limited to devices for which not more than 8,000 individuals per year would be subject to diagnosis by the device in the United States. You may find more information on the HDE program, including a link to the HDE guidance, on FDA's HDE website.

For IVDs offered as LDTs, please refer to the preamble to the LDT final rule and FDA's Laboratory Developed Tests website for additional information regarding applicable requirements and FDA's policy for phasing out the general enforcement discretion approach for LDTs.

CDR Kim Piermatteo: Thanks Toby. So for our next question, that question is, what are FDA's expectations for analytical and clinical validation for an LDT? What standards are appropriate for use during analytical and clinical validation?

Toby Lowe: So as Brittany discussed during the presentation, the analytical and clinical validation for each submission may depend on a number of factors, including the analyte detected, the technology used to measure it, the specific claims made by the manufacturer and the risks of wrong results. To understand the type of validation information FDA may expect to review, FDA encourages the use of the resources in the presentation such as recognized consensus standards, including many CLSI guidelines, the searchable database for FDA recognized consensus standards is linked in the slides, as well as decision summaries that show the type of information that FDA has previously found appropriate to support a 510(k), PMA, or De Novo submission for similar test systems.

FDA also issues a number of guidance documents that may be helpful in gathering data and preparing for a premarket submission, which can be found on our website as well. When manufacturers have specific questions that are not addressed by any of the publicly available resources, they may submit a Pre-Submission, as described in the FDA guidance Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program, which can also be found on our website.

CDR Kim Piermatteo: Thanks again Toby. Okay, moving on to another question and that question is, does FDA expect separate submissions for each analyte on a panel, or is one submission sufficient for a panel with multiple analytes? Is the user fee different for submissions that include multiple analytes?

Toby Lowe: Most often, a single submission will contain only a single device with a single indication for use. However, as described in the FDA guidance Bundling Multiple Devices or Multiple Indications in a Single Submission, found on our website, there are instances where it may be appropriate to combine information supporting multiple devices or multiple indications for use in a single submission. Generally, this occurs when the devices or indications present scientific and regulatory issues that can most efficiently be addressed during one review. In determining whether it can review a bundled submission during the course of one review, FDA may consider whether the supporting data are similar, primarily one review division or group will be involved, and the devices or indications for use are similar.

An example of a multianalyte panel that would be appropriate for a single submission would be a panel of general chemistry analytes, all intended for use on the same clinical chemistry analyzer, and all intended for use in the same patient population. For example, a multianalyte panel including sodium, potassium, and calcium could be submitted as a single submission. Similarly, we have received submissions for a panel of respiratory viruses, such as influenza A, influenza B, and RSV, and drugs of abuse panels that include cocaine, THC, opiates, methamphetamine, amphetamine, etc., in a single submission.

An example of a multianalyte panel that would not be appropriate for a single submission would include a panel with different analytes and with different intended uses that are supported by different types of data. For example, a test to assess risk of developing type 2 diabetes in a population of patients who are

overweight but otherwise healthy and a test to assess risk of kidney failure in patients who have already been diagnosed with moderate kidney disease would not be appropriate for bundling into a single submission.

User fees are based on the submission type such as 510(k), De Novo, and PMA, and are not dependent on the number of analytes or indications included in that submission.

CDR Kim Piermatteo: Thanks again Toby. That was quite a few questions on that one. Okay, so turning to our next question, this question is, is there a fast-track submission pathway for assays currently performed as LDTs under the new rule?

Toby Lowe: The fast-track submission program applies specifically to the review of new drugs and biological drug products, as described in the 2014 Expedited Programs for Serious Conditions – Drugs and Biologics Guidance. However, FDA's Breakthrough Devices program is intended to help expedite the development and review of certain devices that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. Submissions for IVDs designated as Breakthrough Devices receive priority review. More information about the Breakthrough Devices Program, including a link to the Breakthrough Devices Program final guidance, can be found on the FDA's Breakthrough Devices Program webpage.

CDR Kim Piermatteo: Great, thanks Toby. Okay, so for our next question, that is, are tests performed as part of research or clinical trials subject to FDA oversight?

Toby Lowe: Thanks Kim. As discussed in the preamble to the LDT Final Rule, the Investigational Device Exemption requirements under section 520(g) of the FD&C Act and 21 CFR part 812 apply to clinical investigations of devices. However, certain categories of clinical investigations of devices are exempt from most IDE requirements under section 812.2(c), and certain other categories of device investigations are deemed to have an approved IDE application under 812.2(b) if the conditions therein are met. Sponsors and investigators of investigational devices have obligations under the IDE regulations and related regulations such as parts 50 and 56, 21 CFR, of the 21 CFR, regarding protection of human subjects and institutional review boards, respectively. Thus, if a laboratory is a sponsor or investigator of an investigational IVD including a reagent or instrument, that laboratory is responsible for ensuring compliance with all applicable requirements under the FD&C Act and FDA's regulations. Investigational IVDs may include an IVD that was previously labeled research use only, RUO, by a third-party manufacturer, an IVD that was previously labeled by a third-party manufacturer for a use different from the use in the clinical investigation, or an IVD manufactured by a third-party but modified by the laboratory for purposes of the clinical investigation.

As discussed in the preamble to the LDT Final Rule, FDA has generally expected compliance with investigational use requirements for LDTs, though we understand that laboratories often are not complying with them currently. Therefore, we have included these requirements in the phaseout policy. FDA expects compliance with investigational use requirements for IVDs offered as LDTs in Stage 2 of the phaseout, which begins on May 6, 2026.

As discussed in the preamble, FDA notes that investigations of diagnostic devices are exempt from most IDE requirements, provided that certain labeling requirements are met and the testing: is noninvasive, does not require an invasive sampling procedure that presents significant risk, does not by design or

intention introduce energy into a subject, and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. That's in 812.2(c)(3). Additionally, investigations of diagnostic devices that are not significant risk are deemed to have an approved IDE without submission of an IDE application if the conditions in 812.2(b) are met.

FDA has several resources available to help sponsors comply with IDE requirements in the context of clinical investigations of IVDs, including a final guidance document entitled In Vitro Diagnostic (IVD) Device Studies--Frequently Asked Questions, which has been available to stakeholders since June of 2020, and a webpage on Investigational Device Exemptions. FDA is also planning a webinar in 2025 relating to IVDs for investigational use.

CDR Kim Piermatteo: Thanks Toby. Okay so we have some more questions that we'd like to get through with you today that were previously submitted. So Toby, the next question that I have for you is, how should manufacturers evaluate the risk of tests that are marketed and interpreted together? Should this be based on the risk for each individual test or the risk when the tests are considered together?

Toby Lowe: Thanks Kim. As discussed in the preamble to the LDT Final Rule, FDA's device classification processes focus on the risk of the IVD itself and availability of controls to address such risk. In classifying devices, FDA considers, among other things, the device's intended use and indications for use, which includes consideration of the intended patient population. The risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Therefore, FDA considers the risk of a device as it is intended to be used. A manufacturer may design a device in many ways, including as a single test that provides a single result or as a panel of tests that collectively provide a single result.

For example, if a test is intended to detect troponin to aid in the diagnosis of myocardial infarction MI, the risk would be assessed based on the use of the test in aiding the diagnosis of MI. However, if the troponin test is combined with NT-proBNP and CRP to collectively aid in diagnosing the risk of future MI, the risk would be assessed based on the combined use of the tests in aiding the diagnosis of future risk of MI even though some of the analytes in the panel are not traditionally associated with assessment for MI.

CDR Kim Piermatteo: Excellent, thanks Toby. So for this next question this one also has multiple parts, there are three, so the first question, I'll read all three Toby and then I'll turn it over to you. So the first part is, should companies with Class III companion diagnostics, such as oncology tests, continue with their PMA submission plans, or will FDA consider alternative pathways like De Novo or 510(k)? Second part, is there an expectation that Class III companion diagnostics will be reclassified as moderate risk? And part three of this question is, will companion diagnostic devices currently listed as Class III be considered appropriate predicate devices once reclassification has been implemented?

Toby Lowe: Thanks Kim. There's a lot to cover there. For companion diagnostics currently classified as Class III with planned PMA submissions, companies should generally continue with their PMA submission plans unless the classification of the device is changed. If the companion diagnostic has a new intended use, it may be eligible for a De Novo classification if the companion diagnostic meets the criteria for classification into Class II. In such cases, companies may submit a De Novo classification request to potentially classify the device as Class II if it presents low to moderate risk and there is no legally marketed predicate device.

The original classification of a device, including Class III companion diagnostic devices, can be changed through reclassification, for which multiple processes exist in the FD&C Act and FDA's regulations. These processes may include issuing a proposed order or orders, convening a classification panel as appropriate, receiving and considering public comment, and issuing a final order or orders.

On January 31, 2024, FDA announced its intent to initiate the reclassification process for most IVDs that are currently Class III into Class II. FDA aims to complete this reclassification process by November 2027, which would allow manufacturers of certain types of IVDs to seek marketing clearance through the 510(k) pathway. This reclassification initiative includes the majority of infectious disease and companion diagnostic IVDs, such as nucleic acid-based, in situ hybridization, and immunohistochemistry-based companion diagnostics used to select cancer treatments.

FDA intends to continue taking a risk-based approach in the classification of IVDs to determine the appropriate level of regulatory controls and to assess whether a new IVD may be classified into Class I or Class II through De Novo classification and special controls established, rather than being Class III and subject to the PMA pathway. Based on our experience, we believe that special controls could be developed, along with general controls, that could provide a reasonable assurance of safety and effectiveness for most future companion diagnostics and infectious disease IVDs.

A predicate device for purposes of FDA clearance of a 510(k) submission is a legally marketed device. A legally marketed device appropriate to serve as a predicate is a device that was legally marketed prior to May 28, 1976 or a device which has been reclassified from Class III to Class II or Class I, the predicate, or a device which has been found to be substantially equivalent through the 510(k) Premarket Notification process. Once a device has been reclassified from Class III to Class II, it may then potentially serve as a predicate device for future 510(k) submissions for other devices of the same device type, streamlining the regulatory pathway for subsequent devices.

CDR Kim Piermatteo: Thank you Toby for that great information. Okay so our next question is, can an LDT be offered for clinical use pending FDA approval? Does the phaseout policy affect this?

Toby Lowe: In general, IVDs cannot be offered for clinical use before FDA authorization, if authorization is required based on the classification of the IVD. There are certain limited exceptions, for example, investigational use or compassionate use.

On May 6, 2024, FDA published the LDT Final Rule. And the preamble to the LDT Final Rule describes several targeted enforcement discretion policies applicable to specific types of IVDs manufactured by a laboratory, pursuant to which FDA generally intends not to enforce some or all applicable requirements. We have posted a table on our website to help manufacturers better understand FDA's general expectations for IVDs falling within these policies, but we refer you to the preamble for complete details.

Generally, for IVDs offered as LDTs that do not fall within a targeted enforcement discretion policy described in the preamble, compliance with premarket review requirements is expected starting with Stage 4, beginning on November 6, 2027, for high risk IVDs offered as LDTs and Stage 5, beginning on May 6, 2028, for moderate risk and low risk IVDs offered as LDTs that require premarket submission, unless a premarket submission has been received by the beginning of this stage in which case FDA intends to continue to exercise enforcement discretion for the pendency of its review.

CDR Kim Piermatteo: Thanks again Toby. Some great information here. Okay, so I'm going to go down to our next question. We have time, it looks like for maybe one more question and that question is, what are the review timelines and fees for submissions to FDA? Will they be different for LDTs than for other IVDs?

Toby Lowe: As Brittany discussed during the webinar, the Medical Device User Fee Amendments, also called MDUFA, authorizes the FDA to collect user fees for the process for the review of medical devices. The user fee program is negotiated with regulated industry every five years. At the end of these negotiations, FDA commits to specific performance goals and program enhancements and industry commits to providing resources through user fees to support them. This includes goals for FDA to perform our reviews in a specific period of time, with the length of time varying based on the type of submission.

During the current MDUFA V program, FDA aims to complete review of a 510(k) submission within 90 days. For a De Novo submission, FDA aims to complete review within 150 days. And for PMAs, the goal review time is 180 days. If a file is placed on hold, where the FDA has requested additional information from the manufacturer, the time the file is on hold does not count toward the FDA review time, though it does count towards the FDA and Industry's shared outcome goals, referred to as total time to decision.

MDUFA V began in 2022 and expires on September 30, 2027. This is before FDA expects compliance with premarket review requirements for IVDs offered as LDTs under the phaseout policy described in the preamble to the LDT Final Rule. We expect that MDUFA VI will be negotiated and authorized before that time. As noted in the current MDUFA V commitment letter, to the extent that laboratories make submissions regarding LDTs that are covered by the MDUFA V agreement, FDA will treat such LDT submissions no less favorably than other submissions to which MDUFA V performance goals apply. More information on user fee agreements can be found on FDA's website.

CDR Kim Piermatteo: Thanks Toby. That will wrap up our previously submitted questions for today. I'd like to thank everyone who submitted questions in advance of today's webinar, as well as to Toby and her team for developing responses to these questions and presenting them to us today.

Toby I'm going to turn it back over to you for your final remarks.

Toby Lowe: Thanks Kim. And thanks everyone for joining today and for Brittany giving such a great presentation. And thanks to everyone who submitted questions prior to the webinar. We hope that today's webinar has been helpful for you to get to know some of the people that oversee IVDs from the FDA. We hope that today's webinar has also been helpful in understanding FDA's total product life cycle approach and FDA's roles and responsibilities in regulating in vitro diagnostic devices throughout the lifecycle of these products. We look forward to future webinars and hope you will be able to join us for those.

CDR Kim Piermatteo: Great, thanks again Toby and thank you Brittany. So for our attendee's information printable slides of today's presentation are currently available on the CDRH events webpage for this webinar, as well as on CDRH Learn at the link provided on this slide under the section titled In Vitro Diagnostics.

A recording of today's webinar and a transcript will be posted to the webinar webpage and CDRH Learn within the following week. And a screen shot of where in CDRH Learn you can find these materials has been provided on this slide as well.

If you have any additional questions about today's webinar, feel free to reach out to us in DICE at DICE@fda.hhs.gov.

And lastly, as Brittany mentioned at the end of her presentation, our next IVD related webinar on the topic of Registration and Listing Requirements for IVDs, Including LDTs will be held on December 3rd from 1 to 2 PM eastern time. And you can find information on how to attend this upcoming webinar and any of our other webinars on our CDRH Events page at www.fda.gov/CDRHEvents.

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

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