Labeling Requirements for In Vitro Diagnostic Products (IVD), Including LDTs, Under 21 CFR 809.10(b)
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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 stakeholders to provide information on how to comply with labeling requirements for in vitro diagnostic products or IVDs, including Laboratory Developed Tests or LDTs. Today we will focus on the labeling requirements for test systems, under 21 CFR 809.10(b). We will not be covering labeling requirements for other types of IVDs such as collection devices and general purpose reagents during this webinar.

I'd now like to introduce today's presenter, 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.

We'll begin with a presentation from Toby and then address previously emailed questions about today's topic.

Before I turn it over to Toby, 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. 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. And lastly, we have a lot of information to provide you; therefore, we have extended the time for today's webinar. And I'll mention this again later as well but a recording of today's webinar and a transcript will be posted to the webinar webpage and CDRH Learn within a week.

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

Toby Lowe: Thank you, Kim, for the introduction. Good afternoon, everyone. Thank you all for attending our webinar today on labeling requirements for in vitro diagnostic products, including laboratory developed tests, under 21 CFR 809.10(b).

As outlined in the preamble to the LDT final rule that FDA issued on May 6, 2024, FDA is phasing out its general enforcement discretion approach for laboratory developed tests, LDTs, in stages. Under the second stage of the phaseout policy, FDA will expect compliance with labeling requirements, including those under 21 CFR Parts 801 and 809, for most IVDs offered as LDTs by May 6, 2026.

During today's webinar, we will be providing information on labeling requirements under 21 CFR 809.10(b) and how IVD manufacturers have met these requirements. Today's webinar will specifically focus on labeling requirements for test systems.

The learning objectives for today's webinar are to first understand the labeling requirements for in vitro diagnostic products, IVDs, under 21 CFR 809.10(b) and, second, to understand compliance with these labeling requirements for test systems that are IVDs offered as LDTs.

To start, lets discuss where 21 CFR 809.10(b) sits relative to other labeling requirements. Labeling is defined under section 201, subsection (m) of the Federal Food Drug and Cosmetic Act as “all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article.”

The Code of Federal Regulations, CFR, Title 21 describes specific labeling requirements for all medical devices under 21 CFR part 801 as well as specific requirements for in vitro diagnostic products for human use under 21 CFR part 809.

21 CFR 809.10 is a section within part 809 that requires IVD manufacturers to disclose basic facts about an IVD, such as the intended use, limitations, and performance characteristics of the IVD. Within that section, paragraph (b) describes the requirements for labeling that accompanies an IVD and this applies to all IVDs, including LDTs. The focus of this webinar will be on labeling requirements for test systems, under 21 CFR 809.10(b), and will not cover labeling requirements for other types of IVDs such as collection devices and general purpose reagents.

[Background Noise]

Labeling requirements under FDA’s regulations help to ensure that IVD labeling has a consistent set of information critical to understanding the IVD and helping assure the safety and effectiveness of the IVD. For example, these requirements help ensure that IVD labeling describes the intended use of the IVD, how the IVD should be used, who should use the IVD, how well the IVD performs, limitations and warnings for the IVD, and under what conditions the IVD should not be used.

Labeling accompanying an IVD, subject to the requirements of 809.10(b), may include a package insert for a distributed assay kit, or for LDTs, a test protocol, test menu, and/or test report template. As described in the preamble to the final LDT rule, we anticipate that for LDTs, the information required under 809.10 might be encompassed in more than one document, such as the test protocol, test report template, and test menu.

Under section 502, subsections (a) and (c) of the Federal Food Drug and Cosmetic Act, labeling must prominently display all required information and be truthful and non-misleading. An IVD without such labeling would be misbranded.

Labeling accompanying an IVD that is developed by the manufacturer is reviewed by FDA during premarket review, as applicable, kept on file by the manufacturer, and accompanies the IVD during its clinical use. The manufacturer of the IVD is responsible for developing and maintaining labeling that is compliant with applicable FDA labeling requirements, and for making this information available to FDA upon request during an FDA inspection.

As noted on the prior slide, FDA reviews the labeling for some IVDs. In general, IVD manufacturers submit their labeling as part of their premarket submission, and FDA reviews the labeling during the review of that submission. Therefore, for IVDs offered as LDTs that are not exempt from premarket

review, IVD manufacturers will be submitting their labeling as part of their premarket review submission.

Next, for IVDs that are exempt from premarket review, FDA does not generally anticipate receiving premarket review submissions or labeling. FDA also does not generally anticipate receiving premarket review submissions for IVDs that fall within certain enforcement discretion policies described in the preamble to the LDT final rule, such as the policies for certain modified versions of another manufacturer's 510(k) cleared or De Novo authorized test or for non-molecular antisera LDTs for rare red blood cell antigens. As noted earlier, manufacturers of such IVDs are expected to have compliant labeling and maintain it on file.

Finally, as described in the preamble to the final rule, for IVDs that fall within the targeted enforcement discretion policies for LDTs approved by the New York State Clinical Laboratory Evaluation Program, New York State CLEP, LDTs for unmet needs, or "currently marketed IVDs offered as LDTs" i.e., those that were first marketed prior to May 6, 2024, where FDA is intending to exercise enforcement discretion for premarket review, FDA intends to request that manufacturers submit labeling information to the Agency in connection with the listing of the IVD as provided in 21 CFR 807.26(e). This information will help FDA more closely monitor these IVDs and identify those that may lack analytical validity, clinical validity, or safety. FDA may take action where the labeling of an IVD offered as an LDT is in violation of applicable requirements, including where the labeling is false or misleading, and/or the IVD offered as an LDT lacks a reasonable assurance of safety and effectiveness for its intended uses as a result of any such claims that are not adequately substantiated.

Turning back to 809.10(b), there are 15 paragraphs within 809.10(b), as shown here on the screen. The link on this screen will take you to title 21 of the Code of Federal Regulations where the complete requirements under 809.10(b) are described. Most IVD manufacturers, including laboratory manufacturers, choose to include sections in their labeling that align with the paragraphs under 809.10(b)(2) through (13). For example, they do this by including an intended use section, a summary and explanation section, principles of procedure section, etc. The location of the name of the device and name and place of business is typically at the top of the labeling and the date of issuance of the labeling is typically found in a header or footer.

Two of these paragraphs, (5) and (6) apply only to specific types of IVDs, reagents and instruments, respectively. As the focus of today's discussion is labeling for test systems, we will talk a little later in the presentation about how to comply with the requirements in paragraphs (5) and (6) for reagents and instruments in the context of labeling for a test system. The other paragraphs under 809.10(b) apply to all IVDs, including test systems.

First, we will walk through the requirements that are applicable to all IVDs. We will be using examples to walk through the requirements and show how IVD manufacturers have complied with each requirement. Today, we will be using examples of test systems approved under a PMA or a humanitarian device exemption since the labeling for those IVDs are publicly available on FDA's website. Labeling requirements for 510(k)-cleared and 510(k)-exempt IVDs are the same as discussed here; however, FDA does not make the labeling for such IVDs publicly available on FDA's website. In other words, the labeling requirements under part 809 apply to all IVDs, regardless of premarket review requirements.

Please keep in mind that these are examples, using publicly available information, to show approaches manufacturers have used to meet the labeling requirements. Labeling can be presented in various formats not limited to the examples shown here. We encourage you to review other labeling examples from FDA authorized devices, such as package inserts provided with assay kits you may use or labeling available through the medical device PMA database on FDA's website, to help better understand how IVD manufacturers have met IVD labeling requirements for various IVDs.

As noted earlier, we anticipate that for LDTs, the information required under 809.10(b) might be encompassed in more than one document, such as the test protocol, test report template, and test menu. Further, as we walk through the examples, you will see that some manufacturers maintain a primary, or summary, labeling document that contains most of the necessary elements to meet the requirements of 809.10(b), and additional documents that contain more detailed labeling information, including proprietary information that they do not want made publicly available. This is often the case with laboratory manufacturers since a detailed test protocol may not be provided to multiple laboratories. In these situations, the primary labeling document is the document that FDA might make publicly available on our website, such as for approved PMAs, whereas the detailed documents, such as the test protocol, would be maintained confidentially.

Getting started, subsection 809.10(b)(1) requires the proprietary and established name be stated and subsection 809.10(b)(2) requires inclusion of the intended use or uses and the type of procedure. For example, qualitative or quantitative. The intended use is the general purpose or function of the device. While the intended use statements for IVDs have varied in detail, the intended use of an IVD, as seen in the example below, generally have included the analyte being detected or measured, the purpose of the IVD, the disease or condition the device is intended to diagnose, monitor or predict risk of, etc., the test method including the technology, specimen type and types of results reported, the patient population for which the device is intended, and the context of use.

It is important that the intended use statement is clear and complete so that users can understand how the IVD is used and the rest of the information in the labeling relative to the intended use. For example, having a clear understanding of the intended use is critical for users to also understand the IVD's limitations and the performance information for the IVD.

In addition, during FDA's review of an IVD, FDA assesses the IVD's analytical validity, clinical validity, and safety based on its intended use. In the premarket approval pathway, FDA assesses whether there is a reasonable assurance of safety and effectiveness, including whether the benefits outweigh the risks of the IVD, based on its intended use.

As you can see in this example, the intended use clearly states the analyte being measured, BRCA1 and BRCA2 alterations, the purpose of the test system aid in identifying a patient population that is eligible for a specific treatment, the disease or condition, therapeutic response, the test method including specimen type and type of results reported, a qualitative next generation sequencing, using formalin-fixed paraffin-embedded ovarian tumor tissue, the patient population, ovarian cancer patients for whom treatment is being considered, and the context of use, a single site laboratory test system.

The next requirement, 809.10(b)(3) requires a summary and explanation of the test, which must include a short history of the methodology of the test, with pertinent references and a balanced statement of

the special merits and limitations of the method or product. Manufacturers generally include a description of the analyte measured and how it relates to the condition being assessed.

This slide includes an example of the summary and explanation section of an AAV5 total antibody test system used as a companion diagnostic for ROCTAVIAN. As shown on the slide, the summary and explanation section of the labeling includes a summary and explanation of the test system, including the clinical context of the test system, a description of the analyte measured, AAV5 total antibodies, and how the analyte measure relates to the condition being assessed, and a summary of the test system. This section also contains the special merits of the product. The labeling contains, in a warnings and precautions section, important limitations of the test system. Combined, this information as well as other information in the labeling document, provides a balanced statement of the merits and limitations of the product.

The next requirement, 21 CFR 809.10(b)(4), requires the chemical, physical, physiological, or biological principles of the procedure be stated, and any chemical reactions and techniques involved to be explained concisely. This isn't the step-by-step instructions, which are required under 809.10(b)(8), which we will go through in a few slides, but rather an explanation of the underlying scientific mechanisms and techniques used in this test system. This is important for providing users of the test system information on the underlying scientific principles of the test system.

This slide includes an example of the principles of procedure section for a polymerase chain reaction, or PCR, based genetic test system intended to detect KIT D816V mutational status. The blue box highlights the stated biological principles of the procedure, which in this case is genomic DNA detection. The purple boxes highlight the chemical reactions and technique, which in this case is a nucleic acid amplification and detection technique that uses two separate PCR reactions and capillary electrophoresis for PCR product detection.

We will cover requirements for reagents and instruments under 809.10(b)(5) and (6) after we walk through the rest of the 809.10(b) requirements that are applicable to all IVDs. The next requirement we will cover, applicable to all IVDs including test systems is 809.10(b)(7) which requires information regarding specimen collection and preparing for analysis. 809.10(b)(7) requires labeling to state special precautions regarding specimen collection including special preparation of the patient as it bears on the validity of the test, the additives, preservatives, etc., necessary to maintain the integrity of the specimen, known interfering substances, and recommended storage, handling or shipping instructions for the protection and maintenance of stability of the specimen. The requirements within this section are intended to ensure that specimens are collected and prepared under conditions that have been validated as suitable specimens for the test system. These requirements help mitigate risks associated with specimen mishandling that can lead to erroneous test results, helping to ensure that the test system maintains the performance stated within the labeling over the course of its use.

Today, we will use three examples to illustrate this labeling requirement. We will first use parts of the labeling for the FoundationFocus CDxBRCA as an example of how labeling requirements for specimen handling and storage have been met for a single site test system from a laboratory manufacturer. For this test system, the manufacturer chose to meet labeling requirements through the use of multiple documents. They created a primary labeling document that includes most information required under 809.10(b), and other accompanying documents that contain additional labeling information.

As shown on this slide, the primary labeling document for this test points the user to the Test Requisition Form as well as a Specimen Preparation Instructions document, which are all documents that are part of the labeling for this test system. As noted previously, for laboratory developed tests, information required under 809.10(b) might be in multiple documents.

In this example, the manufacturer provides a box for shipping samples to their laboratory. In this box, they include specimen handling and preparation instructions. This document is separate from and in addition to their primary labeling document. This specimen handling document describes: what is considered an acceptable sample for the test system; detailed instructions on how to prepare the samples; and shipping instructions.

Consistent with 809.10(b)(7)(i), this document includes a section with warnings and precautions regarding specimen collection. This section states that biopsy sample collection may pose a risk to the patient when archival tissue is not available.

Consistent with 809.10(b)(7)(ii) and (iii), this document describes how to prepare samples for this test and the additives, preservatives, etc. that are necessary to maintain the integrity of the specimen. Namely that the specimens should be formalin fixed, paraffin embedded. It also includes that other fixatives, which may interfere with the test system, should not be used. It also states that specimens should not be decalcified.

And lastly, consistent with 809.10(b)(7)(ii) and (iv), this document includes the recommended handling instructions for the protection and maintenance of the stability of the specimen. The shipping instructions include information on how to ship the samples which in this case do not require any specialized conditions for shipping.

This slide includes two additional examples of specimen collection and preparation sections from other test systems to illustrate different ways information regarding specimen collection and preparation for analysis could be presented. The example on the left side of the screen is for an AAV5 total antibody test system used as a companion diagnostic for ROCTAVIAN where the specimen is a whole blood sample collected using a 3.2% sodium citrate blood collection tube. As you can see, the test manufacturer includes all information, including the special precautions, additives, preservatives, known interfering substances and recommended storage and shipping instructions in one section. In this example, shipping conditions are specified the samples must be frozen at -10°C or below and shipped on dry ice. The labeling on the right side of the screen, for a human papilloma virus test system, shows an example where the specimen collection and preparation analysis information is divided into subsections for specimen types, specimen storage, specimen shipping, and preparation for analysis.

Now let's move on to 809.10(b)(8), which requires statement of a step-by-step outline of recommended procedures from reception of the specimen to obtaining results. These requirements are intended to help ensure that labeling accompanying an IVD has adequate instructions for performing the IVD. 809.10(b)(8) contains six paragraphs describing the information that must be included within the step-by-step procedures described in the labeling for the test system. This information may be contained in one document or multiple documents. As discussed earlier, for LDTs, most information regarding the procedure is typically contained in the laboratory's test protocol and only high-level information regarding the procedure is included in the primary labeling document. In the case of LDTs with approved PMAs, FDA makes the primary labeling document publicly available through its PMA database; however,

the laboratory's internal test protocol may be confidential or proprietary. We will show multiple examples in the coming slides.

The first example is from a laboratory manufacturer for a single site test system. Looking at the AAV5 DetectCDx from ARUP laboratories, there is high-level information on the steps for performing the test system in the principles of the test procedure section of the labeling. There is also information on the reagents and instruments used in the test system in their own section. While this publicly facing document does not have as much detail as a typical package insert for an assay kit, it does contain the basic elements required under 809.10(b)(8). The laboratory's internal test protocol contains more detailed information, but this is not publicly available.

Next, we will use publicly available examples of package inserts from distributed kits to walk through the detailed procedure information required in each paragraph of 809.10(b)(8). In general, this level of detailed information is contained in a laboratory's test protocol, which may be confidential and proprietary, and has not typically been made public by FDA.

Starting at the beginning, 21 CFR 809.10(b)(8)(i) requires labeling accompanying an IVD to include a list of all materials provided with their instructions for use. 21 CFR 809.10(b)(8)(ii) requires labeling accompanying an IVD to include a list of materials required but not provided. Together, these two requirements ensure that the materials used in the test system are adequately described in the labeling. For the PartoSure Test example, all materials are provided, including the collection swab, test strip, and solvent solution, by the manufacturer in a single kit. For this test system, there are no materials required but not provided. Therefore, 809.10(b)(8)(ii) is not applicable for this test system.

The next example is of a procedure that lists both materials provided for the test system and materials required for the test system but not provided.

Moving on, 21 CFR 809.10(b)(8)(iii) requires that step-by-step procedures include a description of the amounts of reagents necessary, times required for specific steps, proper temperatures, wavelengths, etc. This requirement helps ensure that the labeling provides adequate information for performing each step, including details that are critical to ensure the procedure is performed properly. Going back to the PartoSure Test example, there are seven steps, which include sample collection. The procedure specifies the time the swab should be rinsed by rotating using the solvent solution. It also specifies that results should be read at five minutes and should not be read or interpreted after 10 minutes. Note that, while this example includes a relatively straightforward procedure with only seven steps, some more complex test systems may have procedures that are two to three pages, or longer.

21 CFR 809.10(b)(8)(iv) requires a statement describing the stability of the final reaction material to be measured and the time within which it shall be measured to assure accurate results. In this PartoSure Test example, the labeling indicates that the intensity of the lines may vary and that faint or uneven lines indicate a stable final result. And as noted in the previous slide, the labeling indicates that results should not be read or interpreted after 10 minutes to help assure accurate results.

21 CFR 809.10(b)(8)(v) requires labeling accompanying an IVD to have details of calibration for the IVD, including a description of the preparation of reference samples, use of blanks, preparation of a standard curve, etc. and a description of the range of calibration that includes the highest and the lowest values measurable by the procedure.

The PartoSure Test is a visually read test system and does not require calibration. In this case 21 CFR 809.10(b)(8)(v) is not applicable. We have included a second example on the slide, for the Abbott RealTime IDH1 test system, to show how details of calibration for a test system may be described. In this example, the labeling for the Abbott RealTime IDH1 assay kit references the operations manual for the Abbott m2000rt instrument, an IVD that is required to have its own 809 compliant labeling, where more detailed information on the calibration procedure is located. This section also lists the materials that are necessary for calibration for the Abbott Real Time IDH1 test system, which are five calibration plates.

For LDTs, a laboratory could similarly point to the operations manual for an instrument if that instrument is appropriately labeled for clinical diagnostic use and is being used in accordance with the intended use for which it is legally marketed. As discussed in the preamble to the final rule, LDT manufacturers that use one or more components that are not appropriately labeled for clinical diagnostic use, such as research use only or RUO components, in their IVDs offered as LDTs are responsible for qualifying those components manufactured by another manufacturer, such as instruments, under their own quality system. Therefore, adequate information on calibration for the instrument should be provided in the labeling for the LDT. When using components that are appropriately labeled for clinical diagnostic use and being used in accordance with the intended use for which it is legally marketed, the manufacturer instead point to the compliant labeling provided by the manufacturer of that component.

21 CFR 809.10(b)(8)(vi) requires labeling accompanying an IVD to have details of kinds of quality control procedures and materials required. If there is a need for both positive and negative controls, this is stated. It also requires that satisfactory limits of performance be stated. In the PartoSure example, the quality control is an internal procedure control where a line appears on the test strip if the test system is functioning properly. We have included a second example on this slide, to show a test system for which separate quality control procedures must be performed in the laboratory. The ADVIA Centaur Anti-Hepatitis B antigen assay, which is run on the ADVIA Centaur instrument, includes detailed quality control procedures, including the materials needed for performing the quality control, how often the procedure should be performed, and the satisfactory level of performance for the quality controls, which is stated on the package insert for the separately purchased quality control material.

For LDTs, FDA anticipates that quality control information, as with other labeling information, may be in multiple documents, such as a primary labeling document and/or the laboratory's internal test protocol.

Now, we will move to the next requirement, under 21 CFR 809.10(b)(9), which requires labeling to include information on the results produced by the test system, including explaining the procedure for calculating the value of the unknown. 809.10(b)(9) goes on to require that the labeling give an explanation for each component of the formula used for the calculation of the unknown, and include a sample calculation, step-by-step, explaining the answer. It also requires that values be expressed to the appropriate number of significant figures.

For test systems that do not provide quantitative results, 809.10(b)(9) requires that there be an adequate description of expected results. We are showing an example of a qualitative single site test system: the AAV5 DetectCDx. The results section includes descriptions of positive and negative results.

The next requirement, 809.10(b)(10), requires that the limitations of the procedure be stated, including extrinsic factors or interfering substances affecting results and, if further testing, either more specific or more sensitive, is indicated in all cases where certain results are obtained, the need for the additional test shall be stated. The limitation section often contains information on relevant populations in whom the test system is not validated, and limitations on the performance of the test system related to interfering substances, poor performance at specific parts of the claimed measuring range, or types of variants where performance is poor or not validated for a genetic test system.

As shown in this example for a single site test system from a laboratory manufacturer, the limitations section includes a statement indicating that the test system is intended for in vitro diagnostic use and for prescription use only. It also includes other important limitations of the test system. For example, that the test system does not detect copy number losses/homozygous deletions in the ATM gene.

809.10(b)(11) requires labeling to describe information on the expected values for the test system. Specifically, the range of expected values as obtained with the product from studies of various populations must be stated, how the range was established must be indicated, and the population on which the range was established must be identified.

On the screen we have shown the expected values section of the labeling from two different test systems. For both, the section describes information on the expected values in different populations, how the expected values were established, and the populations used to establish the expected values. For quantitative test systems, this information is most commonly obtained through a reference range study in a healthy population. Depending on the test system, there may be a number of different expected values. For example, as shown on the left side of the screen, there may be different reference ranges for men and women. Test systems may also include different reference ranges for pediatric individuals. For qualitative test systems, this section may describe the cut-off for the device and how patients are expected to be distributed around that cut-off. Or, as shown in the example on the right side of the screen, this has been demonstrated by providing information on the association between test results and different patient populations.

809.10(b)(12) requires labeling to include information on the specific performance characteristics for the test system. This must include, as appropriate, information describing such things as accuracy, precision, specificity, and sensitivity. These must be related to a generally accepted method using biological specimens from normal and abnormal populations. A statement summarizing the data upon which the specific performance characteristics are based must be included.

The specific performance characteristics required to be included in the labeling may include performance characteristics beyond accuracy, precision, sensitivity and specificity, depending on which performance characteristics are relevant for demonstrating the test system's safety and effectiveness. For example, linearity performance is applicable for quantitative test systems. Performance characteristics typically include both analytical and clinical performance.

On this slide, we are showing excerpts of some of the performance characteristics in the labeling for a single site test system from a laboratory manufacturer. Each performance characteristic has its own section. The precision section clearly and concisely describes the study design and data demonstrating the precision of the test system. In this example, the laboratory chose to perform their precision study based on the recommendations in an FDA-recognized Clinical Laboratory Standards Institute standard.

The same is true for other analytical performance characteristics for the test system, such as specificity which was evaluated by testing for interferences and cross-reactivity to other antibodies. In addition, performance characteristics relevant to the test type, such as prozone effect and carryover, are also described.

The last 3 requirements for labeling for IVD products, including test systems, under 809.10(b) require a bibliography of pertinent references keyed to the text, the name and place of the business of manufacturer, packer, or distributor, and the date of issuance of the last revision of the labeling.

Now let's jump back to 809.10(b)(5) and 809.10(b)(6), which include requirements specific to reagents and instruments. Reagents and instruments that are labeled for clinical diagnostic use i.e., labeled for "in vitro diagnostic use" and not labeled for research or investigational use, must have labeling accompanying the product. For example, package inserts that comply with the requirements under 809.10(b)(5) and 809.10(b)(6), respectively, as well as other 809.10(b) requirements, as applicable. As you can see on the slide, which includes excerpts from the full text, there are several requirements for reagents and instruments, respectively. As we move through some examples, we'll discuss the specifics of each of these requirements.

Since today's discussion is focused on the labeling for test systems, let's first look at how the reagent and instrument labeling requirements relate to test system labeling.

Generally, most test systems include reagents and instruments. Therefore, the test systems must comply with the labeling requirements in 809.10(b)(5) and 809.10(b)(6), as applicable. Test systems often use reagents and instruments that are labeled for clinical diagnostic use. Some test systems, including LDTs, that use such reagents and instruments in accordance with their labeled intended use reference the compliant reagent and instrument labeling, rather than repeating the reagent and instrument labeling information in the test system labeling. These reagents and instruments are typically listed in the test system labeling as the materials that are "required but not provided", as required under 809.10(b)(8)(ii).

In contrast, in some cases, test systems use reagents or instruments that are not appropriately labeled for clinical diagnostic use, such as reagents and instruments intended for research use only, or where the reagents and instruments are being used in the test system in a manner that is not in accordance with their labeled intended use. As discussed in the preamble to the LDT final rule, if a laboratory chooses to use one or more RUO components in its IVDs offered as LDTs, then the laboratory is responsible for qualifying such components in its IVDs under their own quality system. As such, the laboratory manufacturer is responsible for complying with the applicable labeling requirements, such as including information in the test system labeling to meet the requirements of 809.10(b)(5) and 809.10(b)(6).

As discussed for other aspects of labeling, for LDTs, FDA anticipates that this information may be contained in more than one document, such as summary information in a primary labeling document and additional details in other documents such as a test protocol or reagent and instrument qualification documentation.

Now, let's look at a couple of examples of labeling meeting the reagent and instrument requirements. First, at the top, there is an example of labeling for a single site test system from a laboratory

manufacturer where, as shown on the slide, high-level information on the reagents and instruments used as part of the test system are described in a primary labeling document. In this example, the laboratory manufacturer has provided information on the primary reagents and their storage conditions, additional reagents used, and the instrument needed for the test system. Laboratories typically include additional detailed information required under 809.10(b)(5) and 809.10(b)(6) in their internal test protocol and other laboratory documents not made public by FDA.

The next example is an assay kit for which all labeling information is publicly available on FDA's website: the Abbott RealTime IDH1 test system. The labeling accompanying the assay kit specifies the complete test system, including the instrument and other reagents that are required for the test system but are not provided with the assay kit.

Under 809.10(b)(5)(i), labeling for reagents is required to have a declaration of the established name, quantity, proportion, or concentration of each reactive ingredient, and for biological material, the source and a measure of its activity. This information must be stated in the system generally used and recognized by the intended user of the reagent. In the example on the slide, this is percentages, milliliters, and units per microliter.

Paragraph 809.10(b)(5)(i) also requires a statement indicating the presence of and characterizing any catalytic or non-reactive ingredients, such as buffers, preservatives, stabilizers. For example, as shown on the slide, the labeling states that the active ingredients are in a buffered solution with preservatives sodium azide and 0.15% ProClin 950.

Paragraph 809.10(b)(5)(ii) requires reagents have a statement of warnings and precautions for users as established in the regulations contained in 16 CFR part 1500 and any other warnings appropriate to the hazard presented by the product, a statement for in vitro diagnostic use, any other limiting statements appropriate to the intended use, and as applicable, a limiting statement appropriate for the intended use of a prescription IVD.

For reagents, statements addressing any hazards or safety precautions for handling the reagent are included in this section. This requirement is intended to help ensure user safety. Looking at the same assay kit example, the publicly available labeling includes warnings regarding reagent handling and a statement that the system is for in vitro diagnostic use.

This next slide shows the remaining requirements under 809.10(b)(5)(ii), limiting statements. As shown here, for the Abbott RealTime IDH1 test system, limiting statements appropriate for the intended use of the reagents in the assay kit are included in a special precautions section, among other places. The labeling for this assay kit also states it is for prescription use only.

Paragraph 809.10(b)(5)(iii) requires adequate instructions for reconstitution, mixing, dilution, etc. for the reagents in a test system. If reconstitution, mixing, diluting, or other manipulation or processing of the reagent is not needed, this requirement is not applicable. As shown in this example, the reagent does not need reconstitution, mixing, or diluting but does need to be thawed in a specific temperature range.

Paragraph 809.10(b)(5)(iv) requires labeling accompanying a reagent to have appropriate storage instructions adequate to protect the stability of those reagents. For products requiring manipulation,

such as reconstitution and/or mixing before use, appropriate storage instructions shall be provided for the reconstituted or mixed product.

This example of labeling for an assay kit includes instructions that the assay reagent kit must be stored at minus 25 to minus 15 degrees Celsius. It also includes instructions for storage of the reagents once they are thawed and mixed with other reagents to form a master mix.

Paragraphs 809.10(b)(5)(v) and 809.10(b)(5)(vi) require labeling accompanying a reagent to have a statement of any purification or treatment required for use and physical, biological, or chemical indications of instability or deterioration, respectively. In the example on the slide, the manufacturer has specified specific thawing conditions as well as indications of instability or deterioration of the reagents.

Now, let's move on to requirements specific to instruments. As with other labeling information for LDTs, FDA anticipates that labeling information specifically required for instruments may be in more than one document, such as a laboratory's test protocol, the instrument's operations manual, or other laboratory documents.

We will walk through the same distributed test system example for instruments as we did for reagents. Paragraphs 809.10(b)(6)(i), 809.10(b)(6)(ii), and 809.10(b)(6)(iii) require statements of the instrument's use or function, installation procedures and special requirements, and principles of operation, respectively. In the example on the slide, the use or function is included in the intended use section, the installation procedures and special requirements are included in the instrument section, and the principles of operation are included in the biological principles of the procedure section. The assay kit labeling here specifies the instrument and other "required but not provided" materials to be used as part of the test system.

The test system labeling refers to the labeling of the Abbott m2000rt instrument, which is sold separately. That instrument is intended for clinical diagnostic use i.e., it is not for research or investigational use, so its labeling is required to comply with all applicable labeling requirements for instruments, including that its label bear a statement that the instrument is "for in vitro diagnostic use." Detailed information about the instrument is included in the instrument's compliant labeling and is not repeated in the test system labeling, which instead refers to the instrument labeling. A similar approach has been taken for labeling for other IVDs that use instruments legally marketed and appropriately labeled for clinical diagnostic use i.e., labeled for in vitro diagnostic use.

Paragraph 809.10(b)(6)(iv) requires the performance characteristics and specifications be stated. The performance characteristics required under 809.10(b)(6) for instruments used in a test system are the same as those described under 809.10(b)(12). As described earlier, 809.10(b)(12) requires labeling include information on the specific performance characteristics for the test system. This must include, as appropriate, information describing such things as accuracy, precision, specificity, and sensitivity. The specific performance characteristics required to be included in the labeling may include performance characteristics beyond accuracy, precision, sensitivity and specificity, depending on which performance characteristics are relevant for demonstrating safety and effectiveness.

For instruments that are already accompanied by compliant labeling, as discussed on the previous slide, the instrument specifications are described in such labeling, such as an instrument manual. Test system labeling using such instruments typically include the instrument labeling by reference as described in the

previous slide. As discussed previously, where LDT manufacturers that are qualifying an instrument that is not accompanied by compliant labeling, for use as part of a test system under their quality system, the laboratory manufacturer is responsible for complying with the applicable labeling requirements, such as including the specifications qualified by the laboratory in the labeling for the LDT to meet the requirements of 809.10(b)(6)(iv). FDA anticipates that this information most often would be in an internal laboratory-specific document and not in a primary labeling document.

Paragraph 809.10(b)(6)(v) requires labeling accompanying an instrument to state the operating instructions for the instrument. As shown on the slide, for the Abbott IDH1 system, the assay kit labeling references the operations manual for the Abbott m2000rt instrument, which includes information specific to how to operate the instrument for the specific IDH1 test system.

Paragraph 809.10(b)(6)(vi) requires labeling accompanying an instrument to state the calibration procedures including materials and/or equipment to be used. As shown on the slide, for the Abbott IDH1 test system, the assay kit labeling references the operations manual for the Abbott m2000rt instrument, which includes the calibration information. This information might look familiar, as it is the same information used in our example on slide 26 for describing the details of calibration as part of a test system procedure.

Paragraphs 809.10(b)(6)(vii), (viii), and (ix) require labeling accompanying an instrument to state the operational precautions and limitations, hazards, and service and maintenance information, respectively. The labeling for the Abbott IDH1 test system references the operations manual for the Abbott 2000rt instrument and states that laboratory personnel must be appropriately trained and follow good laboratory practices.

That concludes our walkthrough of examples of how IVD manufacturers have complied with the labeling requirements under 809.10(b) for labeling accompanying an IVD.

We recognize that we have covered a lot of information in a short time. To summarize, it's important to keep in mind that the labeling requirements under 809.10(b) are intended to help ensure that IVD labeling has a consistent set of information critical to understanding IVDs and helping assure the safety and effectiveness of IVDs. When considering how to develop appropriate and adequate labeling for an IVD, manufacturers often consider the intended use of the IVD and focus on clarity and completeness for the intended user.

Most IVDs offered as LDTs are generally expected to comply with FDA's labeling requirements by May 6, 2026. As described in the preamble to the LDT final rule, there are targeted enforcement discretion policies that may apply to certain IVDs offered as LDTs, and for certain policies, FDA intends to request labeling for those IVDs at the time of device listing.

There are many examples of IVD labeling publicly available on FDA's website that reflect different approaches used to comply with the labeling requirements. As stated in the preamble to the LDT final rule and throughout today's webinar, FDA anticipates that, for LDTs, the required labeling information may be encompassed in more than one document, such as a primary labeling document as well as the test protocol, test report template, and test menu.

And that's the end of today's presentation on labeling for IVDs, including LDTs. We hope that this has been helpful in providing an overview on how to comply with labeling requirements for test systems under 809.10(b).

Our next webinar related to FDA's final rule on LDTs will be October 24, 2024, from 1 to 2 PM ET, and will provide an overview of FDA's Total Product Lifecycle Approach to In Vitro Diagnostic Products. We hope that you will join us for the October and future webinars.

This slide and the next include resources and references mentioned during today's webinar.

CDR Kim Piermatteo: Thank you for that presentation, Toby. And we apologize for the brief interference noise at the beginning of the presentation. We'll now transition to address some of your previously submitted questions related to today's topic. For this segment, I'll read a question aloud and then 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. Our first question today is, FDA has stated that the Agency intends to request submission of labeling for certain IVDs offered as LDTs at the time of device listing. What does this mean, and what is the scope of FDA's review of this labeling?

Toby Lowe: Thanks Kim. For IVDs that fall within the enforcement discretion policies for New York State CLEP, unmet needs, or "currently marketed IVDs offered as LDTs", i.e., those first marketed before May 6, 2024, where FDA is intending to exercise enforcement discretion for premarket review, FDA intends to request that manufacturers submit labeling information to the Agency in connection with the listing of the IVD as provided in 21 CFR 807.26(e).

As described in the preamble to the LDT final rule, labeling includes IVD performance information and a summary of supporting validation, as applicable. In particular, this information will help FDA more closely monitor IVDs offered as LDTs under these enforcement discretion policies, and identify those that may lack analytical validity, clinical validity, or safety, helping with FDA's postmarket oversight for these IVDs. For example, as part of its review of labeling for currently marketed IVDs offered as LDTs, FDA intends to look closely at claims of superior performance and whether those claims are adequately substantiated. FDA generally intends to take action where the labeling of an IVD offered as a LDT is false or misleading, and/or the IVD offered as an LDT lacks the appropriate assurance of safety and effectiveness for its intended uses as a result of any such claims that are not adequately substantiated.

CDR Kim Piermatteo: Thanks Toby. Ok so for our next question, that question is, will enforcement discretion be applied to promotional materials?

Toby Lowe: As described in the preamble to the final rule, FDA expects compliance with labeling requirements for most IVDs offered as LDTs by May 6, 2026. Labeling may include promotional material. The term labeling is defined in the Federal Food, Drug, and Cosmetic Act as including all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers or accompanying such article. Such materials must comply with labeling requirements, including the requirement to be truthful and non-misleading. Labeling that is not truthful or that is misleading would result in the product being misbranded.

As part of its labeling review, FDA also intends to look closely at claims of superior performance and whether such claims are adequately substantiated. Such claims are of particular public health concern because, in FDA's experience, they have led to escalating claims from competitors that can ultimately mislead the public. FDA generally intends to take action where labeling, including promotional materials, for an IVD are false or misleading or where the test lacks appropriate assurance of safety and effectiveness for its intended uses as a result of any claims that are not adequately substantiated.

As described in the preamble to the final rule, FDA generally does not expect compliance with applicable requirements, including labeling requirements, for IVDs offered as LDTs under certain enforcement discretion policies, including 1976-Type LDTs, HLA tests for transplantation, forensic tests, and LDTs manufactured and performed within DoD and VHA.

CDR Kim Piermatteo: Thanks again Toby. So our next question is, what are the FDA's expectations regarding labeling for LDTs?

Toby Lowe: Thanks Kim. Again, as described in the preamble to the final rule, FDA expects compliance with labeling requirements for most IVDs offered as LDTs by May 6, 2026.

The IVD labeling requirements set forth in 21 CFR 809.10(b) specify the information that must be included in labeling accompanying each product, such as a package insert. However, the regulations do not require that the labeling be in the form of a package insert. As described in the preamble, FDA anticipates that, for LDTs, the information required under 21 CFR 809.10(b) might be encompassed in more than one document, such as the test protocol, test report template, and test menu. In FDA's experience to date, most laboratory manufacturers have met the requirements of 809.10(b) by maintaining a document summarizing the information required under 809.10(b), and additional documents that contain more detail, such as the test protocol, test report template, and test menu, which may include proprietary information. In these situations, FDA refers to the summary as the primary labeling document. For PMAs, FDA makes the primary labeling document publicly available on our website, whereas other detailed documents referenced in the primary labeling document, such as the test protocol, would be maintained confidentially.

Manufacturers are responsible for having compliant labeling and maintaining it on file regardless of whether it is submitted to FDA. For IVDs subject to premarket review, proposed labeling is generally required to be submitted as part of a premarket submission.

As described in the preamble to the final rule, for IVDs that fall within certain targeted enforcement discretion policies for which FDA intends to exercise enforcement discretion with respect to premarket review, specifically the targeted enforcement discretion policies for LDTs approved by the New York State Clinical Laboratory Evaluation Program, New York State CLEP, certain LDTs for unmet needs, and "currently marketed IVDs offered as LDTs", i.e., those that were first marketed prior to May 6, 2024, FDA intends to request that manufacturers submit labeling information to the Agency in connection with the listing of the IVD as provided in 21 CFR 807.26(e).

CDR Kim Piermatteo: Thanks again Toby. That was a lot of information. Ok so for our next question that is, what are the labeling expectations for reagents and instruments used as part of an LDT but not manufactured by the laboratory?

Toby Lowe: Thanks Kim. Reagent and instrument specific labeling requirements can be found in 21 CFR 809.10(b)(5) and 21 CFR 809.10(b)(6), respectively. These requirements must be met for any test system for clinical diagnostic use that uses reagents and/or instruments.

Test systems often use reagents and instruments that are labeled for clinical diagnostic use. Some test systems, including LDTs, that use such reagents and instruments in accordance with their labeled intended use reference the compliant reagent and instrument labeling, rather than repeating the reagent and instrument labeling information in the test system labeling. These reagents and instruments are typically listed in the test system labeling as the materials that are "required but not provided", as required under 809.10(b)(8)(ii).

In contrast, in some cases, test systems use reagents or instruments that are not appropriately labeled for clinical diagnostic use, such as reagents and instruments intended for research use only, or where the reagents and instruments are being used in the test system in a manner that is not in accordance with their labeled intended use. As discussed in the preamble to the LDT final rule, if a laboratory chooses to use one or more RUO components in its IVDs offered as LDTs, then the laboratory is responsible for qualifying such components in its IVDs under their own quality system. As such, the laboratory manufacturer is responsible for complying with the applicable labeling requirements, such as including information in the test system labeling to meet the requirements of 809.10(b)(5) and 809.10(b)(6). As discussed for other aspects of labeling, for LDTs, FDA anticipates that this information may be contained in more than one document, such as summary information in a primary labeling document and additional details in other documents such as a test protocol or reagent and instrument qualification documentation.

CDR Kim Piermatteo: Great, thanks Toby. And we have one more question for today. And that question is, what are the labeling expectations around performance characteristics and how does that differ from what is expected to be included in a premarket submission?

Toby Lowe: Thanks Kim. 21 CFR 809.10(b)(12) requires labeling to include information on the specific performance characteristics for the test system. This must include, as appropriate, information describing such things as accuracy, precision, specificity, and sensitivity. These must be related to a generally accepted method using biological specimens from normal and abnormal populations. A statement summarizing the data upon which the specific performance characteristics are based must be included.

The specific performance characteristics required to be included in the labeling may include performance characteristics beyond accuracy, precision, sensitivity and specificity, depending on which performance characteristics are relevant for demonstrating the test system's safety and effectiveness. For example, linearity performance is relevant for quantitative test systems. Performance characteristics typically include both analytical and clinical performance. While labeling for a test system must include a summary of the data, additional details of the validation are generally expected in a premarket submission.

CDR Kim Piermatteo: Thanks again 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'd like to turn it back over to you to provide any final remarks on today's topic.

Toby Lowe: Thanks Kim. I just want to thank everyone again for joining us today. Hopefully this has been helpful to get a better understanding of the labeling requirements for IVDs under 21 CFR 809.10(b) and compliance with these labeling requirements for test systems that are IVDs offered as LDTs. We look forward to future webinars and hope you will be able to join us for those too.

CDR Kim Piermatteo: Thanks again Toby. So for your information, printable slides of today's presentation are currently available on the CDRH events page for this webinar, as well as on CDRH Learn at the link provided on this slide under the section titled "In Vitro Diagnostics."

As I mentioned earlier, 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.

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

And lastly, as Toby mentioned previously, our next IVD related webinar on the topic of FDA's Total Product Life Cycle Approach to IVDs will be held on October 24th from 1 to 2 PM eastern time. You can find information on how to attend this webinar and any of our upcoming webinars on our CDRH Events page and a link to this page is provided at the bottom of this slide.

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

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