DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

JUL 31 2014

The Honorable Tom Harkin
Chairman
Committee on Health, Education, Labor and Pensions
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

As required by Section 1143 of the Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law by the President on July 9, 2012, the Food and Drug Administration (FDA) is providing notification to the Committee on Health, Education, Labor and Pensions and the House Committee on Energy and Commerce of its intent to issue draft guidance entitled *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* (Framework Guidance) and an accompanying draft guidance document entitled *FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)*. The anticipated details of these draft guidance documents are included in this notification and are found in the enclosure to this notification.

The draft Framework Guidance proposes a risk-based, phased-in framework for oversight of LDTs in a manner that is consistent with FDA's current regulation of *in vitro* diagnostic devices. The accompanying draft guidance describes the manner in which laboratories may provide notification and comply with medical device adverse event reporting.

Section 1143 requires FDA to make this notification at least 60 days prior to such issuance of draft or final guidances on the regulation of LDTs, and to include in such notification the anticipated details of such action. For this reason, FDA will not publish the draft guidance documents identified in the notification or establish a docket until at least 60 days after the notification.

Sincerely,

Sally Howard
Deputy Commissioner
Policy, Planning and Legislation

Enclosure

cc: The Honorable Lamar Alexander
Ranking Member
Committee on Health, Education, Labor and Pensions

Members
Committee on Health, Education, Labor and Pensions

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

JUL 31 2014

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Sincerely,

Sally Howard
Deputy Commissioner
Policy, Planning and Legislation

Enclosure

cc: The Honorable Henry Waxman
Ranking Member
Committee on Energy and Commerce

Members
Committee on Energy and Commerce

Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

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Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

This document provides the anticipated details of the *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* that FDA intends to issue in 60 days, and is being provided to Congress pursuant to section 1143 of the Food and Drug Administration Safety and Innovation Act of 2012

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of In Vitro Diagnostics and Radiological Health

Center for Biologics Evaluation and Research

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Framework for Oversight of Laboratory Developed Tests (LDTs)

A. Introduction

This document describes a risk-based framework for addressing the regulatory oversight of a subset of *in vitro* diagnostic devices[1] (IVDs) referred to as laboratory developed tests[2] (LDTs). This document is intended to provide guidance to clinical laboratories that manufacture LDTs about how FDA (the Agency) intends to enforce authorities that apply to such laboratories as medical device manufacturers[3] under the Federal Food, Drug, and Cosmetic Act (the FD&C Act or the Act).

Specifically, this document describes FDA's priorities for enforcing premarket and postmarket requirements for LDTs as well as the process by which FDA intends to phase in enforcement of FDA regulatory requirements for LDTs over time.

This document is not an exhaustive reference for all regulatory requirements under the FD&C Act or FDA regulations that may apply to medical devices, including LDTs.

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[1] Per 21 CFR 809.3(a) *in vitro* diagnostic devices are "those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act."

[2] In the past, LDTs were referred to as "home brew" or "in-house" devices. The term "laboratory developed test" and its acronym "LDT" replaced "home brew" over time, but the regulatory considerations are not affected by the change in terminology.

[3] A manufacturer is any person who engages in the "manufacture, preparation, propagation, compounding, assembly, or processing of a device," defined as "the making by chemical, physical, biological, or other procedures of any article that meets the definition of device in section 201(h) of the act." 21 CFR 807.3(d); *see also* 21 CFR 803.3 (a manufacturer is "any person who manufactures, prepares, propagates, compounds, assembles, or processes a device by chemical, physical, biological or other procedure.").

Omission of discussion of any particular regulatory requirement in this document does not relieve any manufacturer of the duty to comply with that requirement.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

B. LDT Definition and Scope of Guidance

FDA defines the term *laboratory developed test* (*LDT*) as an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory.[4,5] The following is an example of an LDT:

- A laboratory uses peer reviewed articles to guide development of a new diagnostic device. The laboratory uses general purpose reagents and analyte specific reagents combined with general laboratory instruments and develops a testing protocol, that together constitute a test system which is then verified and validated within the laboratory. Once validated this device is used by the laboratory to provide clinical diagnostic results.

FDA does not consider devices to be LDTs if they are designed or manufactured completely, or partly, outside of the laboratory that offers and uses them. The following are some examples of devices that FDA does not consider to meet the definition of an LDT:

- An entity that owns several clinical laboratories develops a device in one of its clinical laboratories and then transfers the device to several clinical laboratories within its network.
- An academic institution develops a device, which it then licenses to or signs an exclusivity agreement with a private corporation that owns a CLIA-certified laboratory. The private corporation's CLIA-certified laboratory then begins manufacturing and using the device to provide clinical diagnostic results.
- A laboratory contracts with a third party manufacturer to produce a key component (e.g., coated microtiter plate, specialized specimen collection kit) used in its device.
- A laboratory contracts with a specification developer to design a new device. Once complete, the design is then transferred to the clinical laboratory for final validation prior to the device being manufactured and used by the laboratory to provide clinical diagnostic results.

[4] FDA generally does not exercise enforcement discretion for direct-to-consumer (DTC) tests regardless of whether they meet the definition of an LDT provided in this guidance. Therefore, the enforcement policies in this guidance do not apply to DTC tests, and FDA's usual enforcement policies apply to DTC tests.

[5] Single laboratory refers to a facility with a single CLIA certificate as described in 42 CFR 493.43(a)-(b). (See also 42 CFR 493.55). LDTs should only be designed, manufactured, and used by laboratories that meet the requirements for high-complexity testing under CLIA as described in 42 CFR 493.17(c)(4) and 493.25.

FDA recognizes that some laboratories may currently be offering devices as LDTs, even though they do not meet FDA's definition of an LDT (e.g., they are not designed, manufactured, and used within a single laboratory). Laboratory tests that are being marketed as LDTs but are in fact not LDTs are out of compliance with the FD&C Act[6]; however, in the interest of ensuring continuity in the testing market and avoiding disruption of access to these tests, FDA intends to apply the same risk-based framework, described in Section D of this document, to any IVD that is offered as an LDT by a CLIA-certified laboratory.

For the purposes of clarity, references to LDTs in Section D of this document include IVDs that are offered by a CLIA-certified laboratory as an "LDT" (whether or not the device meets the FDA's definition of LDT), unless otherwise specified.

C. Background

1. Regulatory History of LDTs

In 1976, Congress enacted the Medical Device Amendments (MDA), which amended the FD&C Act to create a comprehensive system for the regulation of medical devices intended for use in humans. At that time, the definition of a device was amended to make explicit that it encompasses IVDs.[7] The definition of a device applies equally to IVDs manufactured by conventional device manufacturers and those manufactured by laboratories. An IVD, therefore, meets the device definition irrespective of where and by whom it is manufactured. However, since the implementation of the MDA of 1976, FDA has generally exercised enforcement discretion so that the Agency has generally not enforced applicable provisions under the FD&C Act and FDA regulations with respect to LDTs. Enforcement discretion for LDTs developed as a matter of general practice, following the implementation of the 1976 MDA.

The Centers for Medicare & Medicaid Services (CMS) has regulated laboratories, including those that develop LDTs, under the Clinical Laboratory Improvement Amendments (CLIA) (42 U.S.C. 263a) since 1988. CLIA governs the accreditation, inspection and certification process for laboratories. CLIA requirements, however, address different functions than the

[6] As with LDTs, these tests meet the definition of device in the FD&C Act and are subject to FDA regulation.

[7] Section 201(h) of the FD&C Act provides:
(h) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--
(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
(3) intended to affect the structure or any function of the body of man or other animals, and
which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

requirements under the FD&C Act. Namely, CLIA requirements address the laboratory's testing process (i.e., the ability to perform laboratory testing in an accurate and reliable manner). Under CLIA, accreditors do not evaluate test validation prior to marketing nor do they assess the clinical validity of a LDT (i.e., the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient). Under the FD&C Act, the FDA assures both the analytical validity (e.g., analytical specificity and sensitivity, accuracy and precision) and clinical validity of diagnostic tests through its premarket clearance or approval process. In addition to premarket review, FDA requirements provide other controls to ensure appropriate design, manufacture, and safety and effectiveness of the device. As a result, while CLIA oversight is important, it alone does not ensure that LDTs are properly designed, consistently manufactured, and are safe and effective for patients.

2. Evolution of LDT Technology, Marketing, and Business Models and the Need for Increased Regulatory Oversight of LDTs

Since 1976, when Congress clarified that IVDs were medical devices under the FD&C Act and FDA opted to exercise enforcement discretion with respect to LDTs under this authority, the industry has grown and evolved in significant ways, as summarized in the discussion below. FDA finds that in the absence of appropriate oversight of LDTs, there is the potential for increased risk for patients.

In 1976, LDTs were mostly manufactured in small volumes by local laboratories. Many laboratories manufactured LDTs that were similar to well-characterized, standard diagnostic devices, as well as other LDTs that were intended for use in diagnosing rare diseases or for other uses to meet the needs of a local patient population. LDTs at the time tended to rely on the manual techniques used by laboratory personnel. LDTs were typically used and interpreted directly by physicians and pathologists working within a single institution that was responsible for the patient. In addition, historically, LDTs were manufactured using components that were legally marketed for clinical use.[8]

Although some laboratories today still manufacture LDTs in this "traditional" manner, the landscape for laboratory testing in general, and LDTs along with it, has changed dramatically since 1976. Today, LDTs are often used in laboratories that are independent of the healthcare delivery entity. Additionally, today, LDTs are frequently manufactured with components and instruments that are not legally marketed for clinical use and also rely more heavily on high-tech instrumentation and software to generate results and clinical interpretations. Moreover, technological advances have increased the use of diagnostic devices in guiding critical clinical management decisions for high-risk diseases and conditions, particularly in the context of personalized medicine.

[8] For purposes of this guidance, components that are legally marketed for clinical use refer to general purpose reagents, immunohistochemical stains, and other components marketed in compliance with applicable FDA regulatory requirements, e.g., properly labeled for *in vitro* diagnostic use (21 CFR 809.10(a)(4)) and manufactured in compliance with quality system requirements (21 CFR Part 820).

Business models for laboratories have also changed since 1976. With the advent of overnight shipping and electronic delivery of information, including device results, a single laboratory can now provide device results nationally and internationally. Today, many new LDT manufacturers are large corporations that nationally market a limited number of complex, high-risk devices, in contrast to 1976, when hospital or public health laboratories used a wide range of devices that were generally either well characterized and similar to standard devices; used to diagnose rare diseases; or designed specifically to meet the needs of their local patients. Together, these changes have resulted in a significant shift in the types of LDTs developed and the potential risks they pose to patients.[9]

In summary, the FDA has determined that the following attributes of modern LDTs, which are not attributes of the types of LDTs offered in 1976, create potential increased risk for patients in the absence of appropriate oversight. Many modern LDTs are:

- manufactured with components that are not legally marketed for clinical use
- offered beyond local populations and manufactured in high volume
- used widely to screen for common diseases rather than rare diseases
- used to direct critical treatment decisions (e.g., prediction of drug response)
- highly complex (e.g., automated interpretation, multi-signal devices, use of non-transparent algorithms and/or complex software to generate device results)

However, FDA recognizes that, as with all IVDs, there is a wide range of risks associated with the wide variety of LDTs. Thus, FDA believes that a risk-based approach to regulatory oversight of LDTs is appropriate and necessary to protect patient safety. A comprehensive framework that describes FDA's enforcement policy for different classes and categories of LDTs will help provide clarity to LDT manufacturers and protect patients.

3. Gaps in Regulatory Oversight of LDTs

Due to changes in the complexity and use of LDTs and the associated increased risks, as described above, FDA believes the policy of general enforcement discretion towards LDTs is no longer appropriate. Although the CLIA requirements are essential for ensuring that laboratories and their personnel maintain standards of high quality, FDA is concerned that compliance with CLIA regulations alone does not ensure that the diagnostic devices themselves are safe and effective as required by the FD&C Act. Specifically, CLIA regulations:

- Do not assure the safety and effectiveness of LDTs.
    - Under CLIA, the laboratory's analytical validation of a LDT is reviewed during its routine biennial survey, which means that the evaluation of analytical validation occurs after the laboratory has already started testing rather than before it markets a test to the public. Performance of analytical

[9] For further information, *see, e.g.*, Report of the Secretary's Advisory Committee on Genetics, Health and Society, "*U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*" (April 2008), at http://oba.od.nih.gov/oba/sacghs/reports/sacghs_oversight_report.pdf; and FDA materials in support of the 2010 FDA public meeting on the "Oversight of Laboratory Developed Tests," available at http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm.

validation (i.e., proof that the device accurately detects analytes) is required by CLIA regulations for a laboratory's use of its test system in its own laboratory prior to reporting outpatient result, but this is generally only assessed after the device is marketed to the public. Moreover, the routine CLIA survey does not include a review of the clinical validation of a LDT – that is, the accuracy with which the test identifies, measures, or predicts the presence or absence of a clinical condition or predisposition in a patient. Accordingly, there is no assurance that the devices are clinically relevant. Under the FD&C Act, both analytical validation and clinical validation are required and assessed before the devices are offered for clinical use.

- Do not require adverse event reporting, which makes it difficult for regulators to detect devices that are inaccurate, ineffective, or unsafe.
- Do not require removal of unsafe devices from the market.
- Do not assess quality manufacturing of devices, a critical area of device oversight.
    - CLIA regulation focuses on laboratory processes for using devices, rather than on the design and manufacture of the devices themselves.
- Do not require informed consent for patients who participate in LDT clinical studies and do not establish procedures for the conduct of such studies.

The Agency has serious concerns regarding the lack of independent review of the evidence of clinical validity of LDTs. Clinical validity is the ability of a diagnostic device to measure or detect the clinical condition for which the device is intended. Clinical validity is not evaluated under CLIA regulations. LDTs that have not been properly clinically validated for their intended use[10] and are used to make critical clinical decisions potentially put patients at risk of missed or incorrect diagnosis, failure to administer appropriate treatment or administration of potentially harmful treatment with no benefit.

Further, the FDA is aware that, while clinical laboratories perform some level of analytical validation for LDTs to meet CLIA requirements (42 CFR 493.1253(b)(2)), the protocols used for that purpose are not adequate to assure the safety and effectiveness of many LDTs. The CLIA survey process reviews LDT analytical validation data, but this is generally conducted onsite after the device is already in use for providing clinical diagnostic results. CLIA oversight is not designed to ensure that LDTs are appropriately analytically validated for their intended use before the test is used clinically. In addition, CLIA does not require or assess the clinical validity of any test. Accordingly, with respect to LDTs, compliance with CLIA regulations alone does not adequately protect patient safety. FDA premarket review under the FD&C Act and FDA regulations is intended to ensure safety and effectiveness.

FDA is also concerned that under the current policy of enforcement discretion, there is no post-market safety monitoring of serious adverse events associated with the use of LDTs. Although the manufacturer medical device reporting requirements (21 CFR 803.50) apply to

[10] As per 21 CFR 801.4 the term "intended use" refers to the objective intent of the persons legally responsible for the labeling of the device. The intent is determined by their expressions or may be shown by the circumstances surrounding the distribution of the device.

laboratories that manufacture LDTs, given that FDA has generally exercised enforcement discretion over LDTs, adverse event reports for LDTs, including reports of serious injuries potentially related to LDTs, have not been systematically reported or collected.[11]

Additionally, although compliance with CLIA requirements provides assurances that clinical laboratory *practices* are of high quality and that the methodologies selected for clinical use have the capability of providing the quality of results required for patient care (42 CFR 493.1445(e)(1) and 42 CFR 493.1445(e)(3)(i – iii)), these requirements were not developed to provide assurances regarding the design, manufacture, and validation of the diagnostic device itself. In other words, even assuming that quality laboratory practices are in place under CLIA (e.g., personnel are appropriately qualified and test methodology has been appropriately selected), problems with a device would still occur if the device were improperly designed or manufactured, or inadequately validated. As a result, there is no assurance that those LDTs designed and manufactured by a clinical laboratory without premarket review and other elements of oversight are well validated or safe and effective, and there is no adverse event reporting to track if they are not.

FDA is also concerned that LDTs that have not undergone rigorous analytical or clinical review are used without the knowledge of the patient or the treating physician that the device being used is not FDA cleared or approved. In the case where an LDT includes a legally marketed analyte specific reagent (ASR), the laboratory must include a statement on the test report indicating that the test has not been cleared or approved by the Food and Drug Administration (21 CFR 809.30(e)). However, beyond this statement on the test report received only after the test is conducted, there is no requirement that the patient or the physician be directly informed of the nature of the device prior to ordering a test, meaning they may not be aware that the test is an LDT and not FDA cleared or approved. Further, even this limited statement would not generally be included in the test report of an LDT that does not use legally marketed ASRs. As a result, treating physicians and patients who rely on the results from the LDT in making medical treatment decisions may be, and often are, unaware that the analytical and clinical validity of the LDT may not have been evaluated by FDA.

FDA believes that it should modify its policy of enforcement discretion in a risk-based manner to ensure FDA oversight and provide appropriate assurances regarding safety and effectiveness. There have been reports of patient harm and concerns about potential harm due to inaccurate, unsafe, ineffective, or poor quality LDTs.[12] FDA oversight of LDTs

[11] See Section D.4 of this document for further discussion of the medical device adverse event reporting requirements under 21 CFR Part 803.

[12] For example, see Buchen, L. "Missing the mark. Why is it so hard to find a test to predict cancer?" *Nature* **471**, 428-432 (2011), available at www.nature.com/news/2011/110323/full/471428a.html?s=news_rss; and the Report of the Secretary's Advisory Committee on Genetics, Health and Society, "*U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*" (April 2008), at http://oba.od.nih.gov/oba/sacghs/reports/sacghs_oversight_report.pdf.

would provide for independent review and evaluation of LDT clinical and analytical performance and claims, assurances of consistent manufacturing, and postmarket controls.

Premarket review would ensure that LDTs are properly designed and evaluated for analytical and clinical validity in the intended use population, two critical aspects of IVD performance. Increased oversight through enforcement of the standard device manufacturer adverse event reporting requirements would provide for post-market monitoring of LDTs to assist in identifying any new problems with device performance or quality once the device is in use. Further, appropriate quality controls implemented through compliance with the FDA Quality System regulation (QS reg) (21 CFR Part 820) would lead to more robust and reliable design and manufacture of LDTs with less chance of device defects leading to adverse events.

A framework for oversight would also provide for greater patient protections, particularly as they relate to proper informed consent when investigational LDTs are being used in patient management.

For these reasons, the FDA plans to modify its policy of enforcement discretion as described in this document, when finalized.

4. Risk-Based Approach toward Oversight of LDTs

Given the concerns discussed above, the Agency believes it should no longer generally exercise enforcement discretion towards all LDTs. Once finalized and implemented, this guidance document is intended to provide an oversight framework that will assure that devices used in the provision of health care, whether developed by a laboratory or a conventional IVD manufacturer, comply with the appropriate levels of regulatory controls to assure that they are safe and effective. Highlights of the oversight framework are provided below in this section, and further details are provided in Section D of this guidance.

Risk-Based Classification

Medical devices are classified as Class I, II or III based upon the controls necessary to provide a reasonable assurance of the safety and effectiveness of the device, and factors relevant to this determination include the device's intended use, technological characteristics, and the risk to patients if the device were to fail. Class I devices, which are subject only to general controls, generally represent the lowest-risk category of devices, while Class III devices, which are subject to general controls and premarket approval, generally represent the highest-risk devices. Section 513(a)(1) of the FD&C Act (21 U.S.C. 360c(a)(1)).

FDA will rely upon the existing medical device classification system to evaluate the risk of a category of LDTs and, informed by the industry's expressed interest in participating in the discussion of the classification process, will use expert advisory panels to help classify devices not previously classified by FDA, as appropriate. In determining the risk an LDT poses to the patient and/or the user, FDA will consider several factors including whether the device is intended for use in high risk disease/conditions or patient populations, whether the device is used for screening or diagnosis, the nature of the clinical decision that will be made based on the test result, whether a physician/pathologist would have other information about

the patient to assist in making a clinical decision (in addition to the LDT result), alternative diagnostic and treatment options available to the patient, the potential consequences/impact of erroneous results, number and type of adverse events associated with the device, etc. To provide additional clarity, FDA intends to issue draft guidance to describe what the Agency considers generally to be Class I, II or III within 18 months of finalization of this guidance.

LDT Framework

FDA intends to continue to exercise enforcement discretion for all applicable regulatory requirements for:

- LDTs used solely for forensic (law enforcement) purposes.
- Certain LDTs for transplantation when used in CLIA-certified, high-complexity histocompatibility laboratories.[13]

FDA intends to exercise enforcement discretion for applicable premarket review requirements and quality systems requirements, but enforce other applicable regulatory requirements[14] including registration and listing (with the option to provide notification[15]) and adverse event reporting, for:

- Low-risk LDTs (Class I devices).
- LDTs for rare diseases and "Traditional LDTs."[16] These types of LDTs reflect the types of LDTs that existed when the enforcement discretion policy was initially implemented.
- "LDTs for Unmet Needs," when no FDA-approved or cleared equivalent device is available.[17]

For other high and moderate risk LDTs, FDA intends to enforce applicable regulatory requirements, including registration and listing (with the option to instead provide notification[18]), adverse event reporting, premarket review, and quality system requirements, as follows:

- *High-risk LDTs (Class III medical devices)*: Registration and listing (with the option to provide notification) and adverse event reporting begin six months after this guidance is finalized. Premarket review requirements begin 12 months after this guidance is finalized for the highest risk devices[19] and phase-in over 4 years for the

[13] These categories are described below in Section D.2.

[14] Unless otherwise exempted, general controls are applicable to all medical devices regardless of their classification. General controls include, but are not limited to, the provisions of the FD&C Act pertaining to prohibitions on adulteration and misbranding, establishment registration and device listing, premarket notification, banned devices, compliance with certain remedies required through an order issued under section 518 of the FD&C Act (e.g.,notification, repair, replacement and refund), records and reports, restricted devices and good manufacturing practices. Section 513(a)(1)(A) of the FD&C Act (21 U.S.C. § 360c(a)(1)(A)).

[15] Notification is described in Section D.3.

[16] LDTs for rare diseases and "Traditional LDTs" are discussed further below in Section D.5.(a).

[17] "LDTs for Unmet Needs" are discussed in Section D.5.(b).

[18] Notification is described in Section D.3.

[19] Highest risk LDTs are described in Section D.5.(c).

remaining high-risk devices.[20] Devices would remain on the market during review and FDA's consideration of applications. FDA's focus on high-risk devices begins with the following: a) LDTs with the same intended use as a cleared or approved companion diagnostic; b) LDTs with the same intended use as an FDA-approved Class III medical device; and c) certain LDTs for determining the safety or efficacy of blood or blood products.

- *Moderate-risk LDTs (Class II medical devices)*: Registration and listing (with the option to provide notification) and adverse event reporting begin six months after this guidance is finalized. Premarket review requirements begin after the high-risk (Class III) LDTs are completed, meaning 5 years after the guidance is finalized, and phase-in over 4 years.[21] FDA intends to utilize FDA-accredited third party review of premarket submissions as appropriate.

In the framework described in Section D of this document, FDA seeks to provide a reasonable, predictable, and consistent regulatory policy for assuring the safety and effectiveness of LDTs and provide sufficient time for implementation.

Where an LDT's analytes/markers that are measured/assessed have had their clinical validity already established in the literature, FDA believes it may not be necessary for sponsors to conduct extensive new studies to demonstrate clinical validity of the analytes/markers, but the sponsor will need to demonstrate that any changes in technology or methodology that differ from that used in the literature to assess the analyte/marker do not affect the clinical validity of the LDT. FDA intends to work with the laboratory community, the health care professional community, and other stakeholders to identify those LDTs for which the clinical validity of the analyte/marker has already been established in the literature.

In addition, for those LDTs that present moderate risk, FDA intends to work with interested parties to expand the Agency's third party review program to include these types of devices. If successful, FDA believes that most moderate-risk LDTs could be reviewed by a third party reviewer. Under this model, FDA would generally review high-risk LDTs subject to a premarket approval application (PMA) (i.e., Class III medical devices), while accrediting third parties to carry out review of most moderate-risk LDTs requiring a premarket notification (510(k)) submission (generally Class II devices). FDA intends to continue exercising enforcement discretion with respect to applicable *premarket review requirements and quality system requirements* for Class I devices, which present the lowest risk.

Timeline

[20] Based on feedback received from industry, FDA intends to phase in the remaining high-risk LDTs and moderate risk LDTs based on a risk-based prioritization that will be determined through a transparent process including expert advisory panels, as appropriate, and opportunity for public comment. FDA intends to publish the prioritization lists for high-risk LDTs within 24 months of finalization of this guidance and moderate-risk LDTs within 4 years.

[21] See note 19.

Registration and Listing/Notification and Adverse Reporting: Six months after this guidance becomes final, manufacturers of LDTs should notify FDA if they are developing LDTs[22] and must begin to report significant adverse events to FDA,[23] so that problems can be detected and corrected in a timely manner.

Premarket Review: FDA intends to phase-in enforcement of premarket review requirements for relevant LDTs over an extended period of time. LDT categories will be phased-in for enforcement based on risk, and the number and type phased-in at a given time will be commensurate with available agency resources. The phased-in enforcement, starting with the highest-risk devices (described in section D.5. (c)), will begin 12 months after the guidance becomes final.

FDA will prioritize all other LDTs based on risk using a public process, including expert advisory panels as appropriate, and will provide advanced notice with respect to timing of enforcement to manufacturers of LDTs that fall into the high- and moderate- risk categories. Premarket review for the highest risk devices will begin 12 months after this guidance is finalized. FDA expects to announce the priority list for the remaining high-risk devices within 24 months from finalization of the guidance, with enforcement for the initial prioritized group on this list of LDTs beginning no less than 12 months after the announcement of the priority list.[24] FDA intends to complete phased-in enforcement of premarket review requirements for Class III devices first (within a period of 5 years of finalization of the guidance). FDA intends to phase in enforcement of requirements for Class II devices once FDA has completed the phase-in of the Class III devices. FDA expects to announce the prioritization of moderate-risk devices within 4 years of finalization of the guidance and complete phased-in enforcement of premarket regulatory requirements for Class II devices within 9 years of finalization of the guidance.

Under the proposed framework, laboratories that manufacture LDTs would comply with appropriate quality controls in the FDA QS reg (21 CFR Part 820) when a PMA is submitted or FDA issues a 510(k) clearance order for the LDT. Compliance with the QS reg would lead to more robust and reliable design and manufacture of LDTs with less chance of device defects leading to adverse events. The proposed framework for LDTs would also provide for greater patient protections, particularly as they relate to proper informed consent when investigational devices are being used in patient management.

[22] The notification process is described below in Section D.3.
[23] The adverse event reporting requirements are described below in Section D.4.
[24] Note that general categories of high-risk LDTs likely to be prioritized for enforcement of premarket review requirements are detailed in Section D.5.(d).

D. Framework for Regulatory Oversight of LDTs

1. Overview

The framework for regulatory oversight of LDTs discussed below describes FDA's general enforcement priorities for LDTs. As a general matter, FDA proposes a risk-based, phased-in approach, in combination with continued exercise of enforcement discretion for certain regulatory requirements and certain types of LDTs.

The Agency believes that this risk-based, phased-in approach is appropriate for several reasons. First, FDA believes that the health risks associated with LDTs, as with all IVDs, vary with each type of device and the Agency's regulatory activities should, accordingly, be implemented based on risk. Second, a phased-in implementation period is meant to mitigate any unintended and unpredictable consequences of immediately enforcing all applicable requirements, such as potential shortages in the availability of these devices for clinical testing. Further, the Agency recognizes that clinical laboratories may be unfamiliar with FDA regulations, and a phased-in implementation approach will allow those facilities time to learn about the requirements and to develop programs to comply with them.
Regardless of the phase-in schedule and use of enforcement discretion, FDA maintains its authority to take enforcement action if necessary to protect the public health, for example, when the Agency determines that an LDT presents a significant risk to public health. Conversely, the Agency may continue to exercise its discretion by not actively enforcing FDA requirements for longer periods of time than described in this guidance when there are shortages of medically necessary devices or for other compelling reasons.

The main elements of FDA's framework for regulatory oversight include:

- Either notification to FDA of LDTs manufactured by a laboratory or Registration and Listing
- Medical Device Reporting Requirements (MDR) for LDTs (e.g., adverse event reporting)
- Continued enforcement discretion with respect to premarket review requirements for low-risk LDTs, "Traditional LDTs," LDTs used for rare diseases, and "LDTs for Unmet Needs"
- Risk-based, phased-in approach to enforcing the premarket review requirements for other high-risk and moderate-risk LDTs
- Use of clinical literature to support a demonstration of clinical validity, which FDA expects would reduce the need for additional clinical studies to show clinical validity for LDTs where the analytes/markers that are measured/assessed have had their clinical validity established in the literature
- Facilitation of third-party review for many moderate risk LDTs
- Phased-in approach to enforcing the Quality System regulation
- Continued enforcement discretion for premarket review of Class I LDTs

The elements of this framework for regulatory oversight of LDTs are described in detail below, along with their rationale and time frames for implementation.

For those LDTs that are already FDA approved or cleared, it is FDA's expectation that manufacturers will continue to follow the regulations. Manufacturers of tests that are used solely for in-process quality control testing in the manufacture of FDA-regulated articles should consult with FDA to determine applicable regulatory requirements.

2. Continued Enforcement Discretion in Full for Certain Categories of LDTs

FDA intends to continue to exercise enforcement discretion in full for certain categories of diagnostic devices as described below. For the following devices, FDA does not intend to enforce applicable registration and listing (nor is FDA requesting notification), adverse event reporting, premarket review, or quality system requirements:

(a) LDTs Used Solely for Forensic (Law Enforcement) Purposes

FDA intends to continue to exercise enforcement discretion in full for IVDs used solely for forensic (law enforcement) purposes whether or not they are LDTs, consistent with current Agency policy.[25]

(b) LDTs Used in CLIA-Certified, High-Complexity Histocompatibility Laboratories for Transplantation

Consistent with a 2011 recommendation from the Secretary's Advisory Committee on Organ Transplantation, FDA intends to continue to exercise enforcement discretion in full over LDTs used in CLIA-certified, high-complexity histocompatibility laboratories, when those LDTs are used in connection with organ, stem cell, and tissue transplantation:

- to perform high resolution allele typing;
- for antibody screening and monitoring; or
- for the purpose of conducting real and "virtual" crossmatch tests.

These devices are often individualized within each medical facility, e.g., use of reagents that reflect local HLA polymorphisms and patient demographics. They also are rapidly evolving. These attributes raise significant concern that enforcement of

[25] For example, see 65 FR 18230 (April 7, 2000) (final rule for OTC test sample collection systems for drugs of abuse testing) ("However, FDA will continue to exercise its enforcement discretion with respect to the use of these products in the law enforcement setting because there are protections to ensure sample integrity and test accuracy that are not generally available in the home, workplace, insurance and sports settings. The additional protections include the use of rules of evidence in judicial proceedings and the representation of the accused (i.e., the person being tested) through the judicial process."); FDA draft guidance, Premarket Submission and Labeling Recommendations for Drugs of Abuse Screening Tests (Dec. 2003), at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070612.htm ("At this time, FDA will continue to defer oversight of the use of these tests in the forensics (law enforcement) setting to the existing system of legal controls, such as the rules of evidence in judicial proceedings and other protections afforded through the judicial process.").

FDA regulatory requirements for these devices could lead to the unavailability of testing used in transplants to sensitized transplant candidates, and in "virtual crossmatching" of donors and recipients at different locations, and could make desensitization and post-transplant monitoring less available. However, this enforcement discretion policy is limited to LDTs used in organ, stem cell, and tissue transplantation, and does not extend to LDTs used in HLA testing for blood transfusion, which is highly standardized across institutions (see Section D.5.(c)).

3. Notification to FDA of LDTs Manufactured by a Laboratory or Registration and Listing

With the exception of the categories of devices identified above in Section D.2 (forensic (law enforcement) LDTs and certain LDTs used in connection with organ, stem cell, and tissue transplantation), for laboratories that manufacture, prepare, propagate, compound, assemble, or process[26] LDTs, FDA intends to continue to exercise enforcement discretion with respect to registration and listing requirements (21 CFR Part 807) provided that such laboratories notify FDA that they are manufacturing LDTs and provide basic information regarding each of these LDTs. Notification is expected to occur once for each LDT, although if significant changes are made to an LDT, additional notification should be provided.

Collection of such data is critical in the implementation of the risk-based framework described in this guidance given that this data will be used to classify LDTs, inform the classification guidance that FDA intends to issue within 24 months of finalizing this guidance (see "Classification of LDTs" in Section D.5.(d)), and prioritize enforcement of premarket review requirements. Specifically, FDA plans to utilize advisory panels to provide recommendations to the Agency on LDT risks, classification, and prioritization of enforcement of applicable regulatory requirements on certain categories of LDTs, as appropriate. Notification data will be useful for advisory panels in developing these recommendations and for FDA in carrying out the activities described in this guidance (e.g., developing the priority list). Additionally, FDA intends to make the notification data publically available (after removing any information for which public disclosure is prohibited), because FDA believes that this information will be helpful to stakeholders, including industry, patients and physicians.

Laboratories should provide notification information to the FDA within 6 months of the date of publication of the final version of this guidance document with respect to their LDTs on the market on the date of publication of the final version of this guidance document, and any new LDTs on the market in the 6 months following publication of this document. Starting 6 months after publication of the final version of this guidance, laboratories offering new LDTs should provide notification prior to offering the LDT for clinical use. It should be noted that when a laboratory makes a significant change to the marketed intended use of an LDT for which they have previously provided notification, the LDT will be considered by the FDA to

[26] See 21 CFR 807.3(d) for definition of these terms. This guidance document uses "manufacture" to encompass all of these terms.

be a new LDT.[27] Therefore, a new notification should be provided prior to offering that LDT for clinical use; this is especially important for those changes in marketed intended use that increase the risk of the device. Additionally, following initial notification, FDA urges laboratories that make other significant modifications to LDTs after notification to re-submit notification data to FDA to communicate such changes (see section D.5.(e) of the guidance for additional information on significant device modifications). Given that notification data will be used to classify LDTs and prioritize enforcement of premarket review requirements based on risk, it will benefit laboratories to provide the most accurate information possible to ensure that appropriate classification is made.

This notification does not constitute compliance with registration and listing requirements, nor will the laboratory be considered to be registered or to have listed its devices with the FDA. Therefore, such laboratories are not required to submit registration fees to FDA with the notification.

Laboratories that do not opt to notify the Agency that they are manufacturing LDTs or provide basic information regarding each of the LDTs manufactured in their laboratory within the abovementioned timeframes will have opted not to be within the scope of FDA's enforcement discretion policy with respect to the registration and listing requirements. Such laboratories would fall within the agency's normal enforcement approach with respect to the registration and listing requirements. Registration and listing requirements include registration of each establishment[28] with the FDA and listing of the devices manufactured in these facilities (21 CFR 807.20(a)). Submission of the registration and listing information must be accompanied by payment of the registration fee (Section 738(a)(3) of the FD&C Act (21 U.S.C. 379j(a)(3))).

Further, FDA does not intend to enforce registration and listing requirements for an establishment that manufactures, prepares, propagates, compounds, assembles or processes one or more LDTs until a premarket submission (e.g., PMA (21 U.S.C. 360e(c); 21 CFR Part 814) or a 510(k) submission (21 U.S.C. 360(k); 21 CFR Part 807, Subpart E)) has been made to the Agency for any one LDT.

Proposed specific instructions on how laboratories should appropriately notify the FDA regarding LDT manufacture and provide basic information regarding the LDTs are provided in the draft guidance document titled "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)."

The notification system described above will be a critical element of the LDT oversight framework, as it will provide the Agency with the necessary information on the LDTs being currently manufactured by clinical laboratories to assist the Agency in implementing the

[27] For purposes of this guidance, FDA uses the term "marketed intended use" to refer to the use(s) of a test that a laboratory promotes or includes in any applicable labeling. Although FDA generally considers new devices to include other types of modifications to an existing device (e.g., technological changes), for the purposes of this subsection only, new LDTs do not include other types of modifications to an existing LDT.
[28] See 21 CFR 807.3(c) for definition of "establishment."

enforcement of premarket requirements for LDTs based on their risk, as described below in Section D.5.

FDA does not intend to exercise enforcement discretion with respect to registration and listing requirements for an establishment that manufactures, prepares, propagates, compounds, assembles or processes medical devices other than or in addition to LDTs, even if the establishment is a laboratory.

4. Medical Device Reporting (MDR) Requirements

With the exception of the categories of tests identified above in Section D.2 (forensic (law enforcement) LDTs and certain LDTs used in connection with organ, stem cell, and tissue transplantation), FDA intends to enforce the manufacturer reporting requirements of the Medical Device Reporting (MDR) regulation (21 CFR Part 803, Subpart E) for laboratories manufacturing LDTs.[29] The MDR regulation requires the manufacturer of a medical device to submit reports to the FDA whenever they become aware[30] of information that reasonably suggests that a device they market may have caused or contributed to[31] a death or serious injury,[32] or has malfunctioned and the malfunction would be likely to cause or contribute to a reportable death or serious injury should it recur. 21 CFR 803.50.

One objective of the MDR regulation is to provide a mechanism for FDA and device manufacturers to identify and monitor significant adverse events involving medical devices so that problems may be detected and corrected in a timely manner. This information is particularly important in the case of LDTs, as many of these devices have not undergone premarket review. MDR reporting for LDTs will provide for an important risk mitigation measure to detect, track, and help address serious problems related to LDT performance should they occur.

Therefore, beginning six months following publication of the final version of this guidance document, FDA intends to cease its exercise of enforcement discretion with respect to the MDR reporting requirements in 21 CFR Part 803, Subpart E, for laboratories that manufacture LDTs. A description of the specific requirements in 21 CFR Part 803, Subpart

[29] With respect to clinical laboratories, FDA has already been enforcing the provisions of the MDR regulation applicable to device user facilities (21 CFR 803.3 and Subpart C). User facilities are required to report to FDA information that reasonably suggests that a device has caused or contributed to the death of a patient and to the manufacturer information that reasonably suggests a device may have caused or contributed to a death or serious injury (21 CFR 803.30).

[30] A manufacturer has "become aware" of an event when an employee of the entity required to report has acquired information to reasonably suggest a reportable adverse event has occurred. (21 CFR 803.3).

[31] The term "caused or contributed to" means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, malfunction, improper or inadequate design, manufacture, labeling, or user error. (21 CFR 803.3)

[32] "Serious Injury" means an injury or illness that is life-threatening, results in permanent impairment of a body function or permanent damage to a body structure, or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. (21 CFR 803.3)

E, as well as further information on how the MDR requirements apply to laboratories is described in the guidance document "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)."

5. Premarket Review Requirements

With the exception of the categories of devices identified above in Section D.2 (forensic (law enforcement) LDTs and certain LDTs used in connection with organ, stem cell, and tissue transplantation) and those identified in paragraphs (a) and (b) below, FDA intends to phase in the enforcement of applicable premarket requirements over time based upon the risk associated with that device. FDA intends to focus its efforts on the highest risk devices first and gradually phase in enforcement for other devices over time. In this manner, it is FDA's intention to avoid undue disruption of medical testing while seeking to assure patient safety and to assure that health care practitioners are relying on device results that are meaningful and accurate when making medical decisions.

(a) Continued Enforcement Discretion with Respect to Premarket Review Requirements for LDTs Used for Rare Diseases and "Traditional LDTs"

The FDA believes that it is appropriate to continue to exercise enforcement discretion with respect to premarket review requirements for the two categories of LDTs described below. However, laboratories that manufacture these LDTs should notify the FDA as described in Section D.3 of this guidance and in the guidance document, "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)." FDA intends to enforce registration and listing requirements for laboratories that manufacture these LDTs if they have not notified the Agency, as described above. In addition, FDA intends to enforce the MDR reporting requirements, including 21 CFR Part 803, Subpart E, for laboratories that manufacture these LDTs, as described in Section D.4 of this document.

LDTs Used for Rare Diseases

The Humanitarian Use Devices (HUD)/Humanitarian Device Exemption (HDE) provisions of the Act (21 U.S.C. 360j(m)) and regulations (21 CFR 814, Subpart H) provide an abbreviated regulatory pathway as an incentive for the development of devices for use in the treatment or diagnosis of rare diseases or conditions.

FDA recognizes that some LDTs may qualify as HUDs. An IVD device may qualify for HUD designation when the number of persons who may be tested with the device is fewer than 4,000 per year. FDA recognizes that one patient may be tested multiple times with the same device; when this occurs, the multiple uses are counted as one use for purposes of defining which devices may qualify as HUDs.

If an IVD is being developed to diagnose or to help diagnose a disease or condition with an incidence of fewer than 4,000 patients per year, but there are more than 4,000 patients a year who would be subject to testing using the device, then the device does not qualify as a HUD (21 CFR 814.102(a)(5)).

While FDA encourages laboratories manufacturing LDTs for rare diseases to seek approval under the HDE provisions, FDA plans to continue to exercise enforcement discretion with regard to premarket review requirements for LDTs that meet the definition in this guidance and the definition of an HUD under 21 CFR 814.102(a)(5).

Traditional LDTs

FDA intends to continue to exercise enforcement discretion with respect to premarket review requirements for "Traditional LDTs," which are those IVD devices that reflect the types of LDT available when FDA began its policy of generally exercising enforcement discretion over LDTs in 1976. In considering whether to exercise enforcement discretion for Traditional LDTs, FDA intends to consider the following factors:

(1) Whether the device meets the definition of LDT in this guidance (a device designed, manufactured and used by a single laboratory); and
(2) Whether the LDT is both manufactured and used by a health care facility laboratory (such as one located in a hospital or clinic) for a patient that is being diagnosed and/or treated at that same health care facility or within the facility's healthcare system[33]; and
(3) Whether the LDT is comprised of only legally marketed components and instruments (e.g., analyte specific reagents (21 CFR 864.4020), general purpose reagents (21 CFR 864.4010), and various classified instruments); and
(4) Whether the LDT is interpreted by qualified laboratory professionals, without the use of automated instrumentation or software for interpretation.

FDA believes that the factors described above help to mitigate the risks associated with these LDTs in several ways. First by meeting the definition of an LDT in this guidance, the laboratory that develops and validates an LDT is the same location with the personnel and appropriate expertise needed to run and interpret the test result. Further, the manufacture and use of LDTs within a facility's healthcare system ensures common responsibility for patient outcomes that may result from the clinical decisions informed by those device results, while providing patient access to any LDT used in a laboratory within that healthcare system. Also, the factors for Traditional LDTs ensure a certain level of quality through the use of only legally marketed components and instruments. When these three factors are in place and CLIA regulations ensure that laboratory personnel are appropriately qualified and trained for their role in the laboratory, FDA believes that the circumstances described

[33] The term "healthcare system" refers to a collection of hospitals that are owned and operated by the same entity and that share access to patient care information for their patients, such as, but not limited to, drug order information, treatment and diagnosis information, and patient outcomes. Please note that in this case, FDA does not consider a contracted diagnostic laboratory to be included in the facility's healthcare system. FDA would consider an owned and operated diagnostic laboratory to be included in the facility's healthcare system. Please also note that the term "hospital" is defined as: "a distinct entity that operates for the primary purpose of providing diagnostic, therapeutic (such as medical, occupational, speech, physical), surgical, and other patient services for specific and general medical conditions. Hospitals include general, chronic disease, rehabilitative, psychiatric, and other special-purpose facilities." 21 CFR 803.3.

above allow for appropriate controls to manage risks specifically related to manual techniques and interpretation in Traditional LDTs. In contrast, automated instrumentation and use of software requires appropriate instrument and software validations to be performed, which are not evaluated under the CLIA regulations. FDA believes that where an LDT relies on manual interpretation by qualified laboratory professionals, rather than the use of automated instrumentation or software for interpretation, and the other factors above are also present, it is appropriate and consistent with the LDTs available when FDA initiated its policy of enforcement discretion over these devices in 1976. FDA believes that these factors appropriately mitigate risks associated with Traditional LDTs being used on patients so that continued enforcement discretion with respect to premarket review requirements is appropriate.

(b) Continued Enforcement Discretion with Respect to Premarket Review Requirements for "LDTs for Unmet Needs" When No FDA-cleared or -approved Alternative Exists

FDA recognizes the role that LDTs can play in meeting urgent unmet healthcare needs. FDA believes it is important to maintain the availability of LDTs that serve unmet needs (but that are not LDTs for rare diseases or "Traditional LDTs") until a comparable FDA-cleared or -approved device becomes available. For this reason, FDA intends to exercise enforcement discretion with respect to premarket review requirements for "LDTs for Unmet Needs." In determining whether an LDT is an "LDT for Unmet Needs," FDA intends to consider the following factors:

(1) Whether the device meets the definition of LDT in this guidance (a device designed, manufactured and used by a single laboratory); and
(2) Whether there is no FDA cleared or approved IVD available for that specific intended use; and
(3) Whether the LDT is both manufactured and used by a health care facility laboratory (such as one located in a hospital or clinic) for a patient that is being diagnosed and/or treated at that same health care facility or within that facility's healthcare system.

For LDTs for Unmet Needs, FDA does not intend to consider factors such as whether the LDT is comprised of only legally marketed components and instruments or whether the LDT is interpreted by qualified laboratory professionals, without the use of automated instrumentation or software for interpretation. FDA believes that greater flexibility is appropriate for LDTs for Unmet Needs because there is no FDA-cleared or approved alternative for the device on the market.

As with Traditional LDTs, FDA believes that the manufacture and use of LDTs for Unmet Needs within a facility's healthcare system will help to mitigate risks because the healthcare system manufacturing and using the test is also responsible for treating the patient, and is thereby responsible for patient outcomes that may result from the clinical decisions informed by that device result.

Note: However, once FDA clears or approves an IVD for the same intended use, FDA will no longer consider the LDT to be an "LDT for Unmet Needs." Therefore, following FDA clearance or approval of a device with the same intended use as an LDT for Unmet Needs, FDA intends to enforce the premarket review requirements if the LDT falls within FDA's enforcement priorities. For example, if the LDT is Class III, then it falls within the initial priorities described in Section D.5.(c), meaning that if FDA approves a Class III test, laboratories offering LDTs with the same intended use would be expected to submit a premarket approval application within 12 months.

If the LDT is Class II and not within one of the categories described in Section D.5.(c), then FDA intends to enforce following the process for prioritizing the Class II LDTs as described in Section D.5.(d), meaning that FDA intends to enforce premarket review when the LDT category is called in and FDA clears a test in that category. FDA will provide adequate public notice through the priority list discussed in Section D.5.(d) that would describe when a new category of LDT is being called in, after which the laboratory will have 12 months to submit a premarket application for their LDT if FDA clears a test in that category. If the appropriate premarket submission is made within the 12-month period, FDA intends to continue to exercise enforcement discretion while that submission is under Agency review to ensure continued availability of the device until FDA makes a final decision on the submission.

Given that laboratories should have already conducted appropriate studies to demonstrate analytical and clinical validity or be able to reference support in the literature to justify device use for clinical decision-making, FDA does not anticipate that submission of a premarket application to FDA for these tests would be overly burdensome. Exercising enforcement discretion with respect to LDTs for Unmet Needs until a device with the same intended use is cleared or approved would encourage the makers of such LDTs to gather appropriate data, without delaying patient access in the absence of a cleared or approved diagnostic device. It also would provide patients and providers with the confidence that once a test is cleared or approved by FDA, all such devices, regardless of who makes them, are safe and effective because all such devices will need to comply with premarket review requirements.

Laboratories that manufacture one or more LDTs for Unmet Needs should notify the FDA, as described in Section D.3 of this guidance. FDA intends to enforce registration and listing requirements for laboratories that manufacture these LDTs if they have not opted to notify the Agency, as described above. In addition, FDA intends to enforce the MDR reporting requirements, including 21 CFR Part 803, Subpart E, for laboratories that manufacture these LDTs, as described in Section D.4 of this document.

(c) Enforcement of Premarket Submission Requirements for Companion Diagnostics and Other High-risk Diagnostic Device Category LDTs

FDA intends to initially focus its enforcement priorities by generally enforcing the premarket review requirements beginning 12 months after this guidance is finalized for the following LDTs: a) LDTs with the same intended use as a cleared or approved companion diagnostic[34]; b) LDTs with the same intended use as an FDA-approved Class III medical device; and c) certain LDTs for determining the safety or efficacy of blood or blood products.

FDA believes that these diagnostic device categories are among the highest risk LDTs currently available on the market because the device either is used to direct patient therapy (as in the case of LDTs with the same intended use as a cleared or approved companion diagnostic) or has the same intended use as a device that FDA has already determined to be in the highest risk classification (Class III).

For 12 months following publication of this guidance document in final form, FDA intends to exercise enforcement discretion with respect to premarket review requirements for currently marketed LDTs in the three abovementioned categories. FDA intends to begin enforcing premarket review requirements for these categories of currently marketed LDTs at the end of that 12-month period. If the appropriate premarket submission (generally a PMA) is made within the 12-month period, FDA intends to continue to exercise enforcement discretion while the premarket submission is under FDA review, so as not to interrupt patient access. FDA intends to begin enforcing premarket review requirements immediately upon publication of this guidance document in final form for all new LDTs (i.e., those that become available for patient testing after final publication of this guidance document) in these categories. FDA will expect manufacturers of these new LDTs to make an appropriate premarket submission and obtain approval or clearance for their devices prior to use.

Blood Donor, Transfusion Compatibility, and HCT/P Donor LDTs

Devices used for blood donor screening are regulated by the Office of Blood Research and Review (OBRR) in the Center for Biologics Evaluation and Research (CBER). FDA regulations require that blood donor screening testing be performed, and that the donor screening devices used be "approved for such use" and performed "in accordance with the manufacturer's instructions" (21 CFR 610.40(a), (b)). For some time now, FDA has enforced these regulatory requirements with respect to LDTs that are donor screening devices.

FDA considers other devices used in determining the safety or efficacy of blood or blood products to be high-risk devices, including devices used for HLA testing for transfusion compatibility and those used for blood donor infectious disease

[34] Companion Diagnostics (also referred to as in vitro companion diagnostic devices or IVD companion diagnostic devices) are those tests intended for use with a corresponding therapeutic product to meet its labeled safety and efficacy claims (e.g., selection of therapy, therapy dosing) and are included in the labeling of the corresponding therapeutic products. Further information regarding companion diagnostics can be found in the draft guidance document entitled "In Vitro Companion Diagnostic Devices."

supplemental or confirmatory testing, or for red blood cell compatibility testing (i.e., phenotyping and/or genotyping of donors and recipients or mother and fetus). As such, similar to the other high-risk LDTs noted above, FDA intends to begin enforcing premarket review requirements for these types of devices at the end of 12 months of the finalization of this guidance.

The regulations also require that donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps) be screened for evidence of relevant communicable diseases using licensed, approved, or cleared donor screening devices (21 CFR 1271.80). FDA intends to continue to enforce this requirement for HCT/P donor screening devices, including for any LDTs intended for this use.

(d) Phased-In Enforcement of Premarket Requirements for Other LDT Categories

After FDA collects and analyzes notification data, it will prioritize the remaining device categories based on risk using a public process. FDA plans to utilize advisory panels to provide recommendations to the Agency on LDT risks and prioritization of enforcement of applicable regulatory requirements on certain categories of LDTs, as appropriate. FDA intends for there to be ample opportunity for public comment.

FDA intends to provide adequate notice about the risk-based prioritization of categories of LDTs to increase transparency and so that laboratories may be able to prepare well in advance of enforcement. FDA anticipates that this phased-in enforcement of premarket review requirements for LDTs will take place over a number of years.

For the high risk devices identified in section (c), FDA intends to begin enforcing premarket review requirements 12 months after this guidance is finalized. FDA expects to announce the priority list for the remaining Class III LDTs within 24 months from finalization of this guidance. In the priority list, FDA plans to describe the order in which the Agency intends to enforce the Class III LDT categories and when the Agency intends to start enforcing the different categories. FDA intends to start enforcing the premarket review requirements for the Class III LDT categories in the highest priority group beginning no less than 12 months after the priority list is announced.[35] If a premarket submission (i.e., PMA (21 CFR Part 814) or biologics license application (BLA) (21 CFR Part 601)) or if appropriate, an investigational device exemption (IDE) (21 CFR Part 812), is submitted within the 12-month period, FDA intends to continue to exercise enforcement discretion while the submission is under FDA review. After FDA begins enforcing the premarket review requirements for LDTs in a particular category, FDA will expect laboratories that develop new LDTs in these categories to comply with premarket review requirements before marketing of such LDTs.

[35] Note that general categories of high-risk LDTs likely to be in the highest priority group for prioritized for enforcement of premarket review requirements are detailed below in this Section under the heading "LDTs of Higher Concern to the Agency."

FDA intends to complete phased-in enforcement of premarket review requirements for Class III devices first (within a period of 5 years of finalization of the guidance). FDA intends to phase-in enforcement of premarket review requirements for Class II devices once FDA has completed the phase-in of the Class III devices. FDA expects to announce the enforcement prioritization of Class II devices within 4 years of finalization of the guidance and complete phased-in enforcement of premarket regulatory requirements for Class II devices within 9 years of finalization of the guidance.

It should be noted that the Agency will accept premarket submissions for LDTs at any point for those laboratories seeking to come into regulatory compliance, even prior to FDA enforcing premarket review requirements for those laboratories' LDT devices.

Classification of LDTs

To provide additional clarity, FDA intends to issue guidance to describe what the Agency considers generally to be Class I, II or III within 24 months of finalization of this guidance.[36]

FDA intends to enforce premarket submission requirements beginning with highest risk LDTs (i.e., FDA intends to address the highest risk Class III devices before addressing lower risk Class II devices). FDA intends to continue exercising enforcement discretion with respect to applicable premarket submission requirements for LDTs that are Class I devices, which present the lowest risk. Once enforcement of a set of LDTs has been completed, FDA intends to enforce premarket submission requirements for the next set of LDTs (based on their risk). The appropriate type of premarket submission (i.e., PMA, 510(k), *de novo*, etc.) will depend on the device classification.

FDA recognizes that some LDTs with new intended uses may automatically be classified in the highest risk class, Class III, as a matter of law. Section 513(f)(1) of the FD&C Act (21 U.S.C. 360c(f)(1)). Where warranted, FDA plans to down classify such LDTs into the appropriate lower risk class on its own initiative or using the *de novo* process, with input from advisory panels where appropriate. Section 513(b)(1), 513(f)(2), and 513(f)(3) of the FD&C Act (21 U.S.C. 360c(b), 21 U.S.C. 360c(f)(2), and 21 U.S.C. 360c(f)(3)).

LDT Devices of Higher Concern to the Agency

FDA has identified several categories of LDTs that have not yet been classified that it believes generally pose a higher risk to patients than other LDTs, and for which

[36] FDA intends to issue a draft version of this guidance for comment prior to an advisory panel meeting on LDT risks and enforcement prioritization.

enforcement of premarket review requirements likely commence earlier (following adequate public notice as described above), as follows:

(1) Devices that act like companion diagnostics.
These diagnostics include those devices that claim to enhance the use of a specific therapeutic product, through selection of therapy, patient population, or dose, but which are not included in the therapeutic product labeling (e.g., devices developed by laboratories that claim to predict who will respond to a therapy approved for use in a larger population). FDA believes these devices represent higher risk to patients given that they provide a direct, often standalone, recommendation for use of a specific therapeutic product that is not supported by the therapeutic product labeling.

(2) Screening devices for serious diseases and/or conditions intended for use in asymptomatic patients with no other available confirmatory diagnostic product or procedure, such as screening device for malignant cancers

(3) Diagnostic devices for certain infectious diseases with high-risk intended uses[37]

(e) Modifications to FDA Cleared/Approved Devices

As in the case of any other entity, a clinical laboratory that modifies an FDA cleared/approved device in a way that affects device performance or intended use is considered to be a device remanufacturer (21 CFR 820.3(w)). Such modifications may include change in specimen type or sample matrix (e.g., saliva vs. whole blood), type of analysis performed (e.g., qualitative vs. quantitative), the purpose of the assay (e.g. screening, diagnosis, prognosis, monitoring, surveillance, and confirmation), the target population(s), etc. These modified devices must meet premarket submission requirements under 21 CFR 807.81(a)(3) and 21 CFR Part 814. FDA intends to begin enforcing premarket requirements for these modified devices as the Agency begins enforcing premarket requirements for the LDT category under which the modified device falls.

(f) Clinical Investigations

FDA intends to continue to enforce investigational device requirements under 21 CFR Part 812 for all clinical investigations of LDTs that are conducted under clinical protocols that require institutional review board approval. Before conducting an investigation, clinical laboratories must follow applicable requirements in 21 CFR Part 56 for institutional review board (IRB) approval as well as applicable

[37] Diagnostic devices for certain infectious diseases with high-risk intended uses are considered to be of higher concern to the Agency. For example, currently available cytomegalovirus and/or Epstein-Barr virus serological devices, intended to detect and differentiate the presence of viral antibodies or antigens to diagnose a viral infection, are generally considered low-risk devices. However, new molecular devices intended to monitor levels of cytomegalovirus or Epstein-Barr virus in infected, immunocompromised, or transplant patients are expected to fall into a higher-risk category because patients in these categories are at greater risk of death from infection, especially if a false negative or low viral load is recorded by the test at the beginning of treatment.

requirements in 21 CFR Part 50 for informed consent from the study subjects at the time of their enrollment in the study. See "In Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions," http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071230.pdf. Currently, the vast majority of IVD development programs involve studies that are considered "exempted investigations" as defined in 21 CFR 812.2. However, if the LDT to be studied in the investigation meets the 21 CFR 812.3 definition of a "significant risk device," the investigation can only be conducted under an approved investigational device exemption (IDE). 21 CFR 812.2. IDE requirements include labeling the LDT for investigational use in accordance with 21 CFR 809.10(c) or 21 CFR 812.5, as applicable, if the laboratory intends to conduct an investigation to pursue FDA clearance or approval.

Further information regarding investigational device requirements can be found on the FDA website at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm

(g) Evaluation of Clinical Validity of LDTs

FDA expects that for many LDTs, clinical validity has already been established in literature. FDA emphasizes that it is the Agency's practice to leverage such information from the literature in lieu of requiring additional studies to demonstrate clinical validity. In these cases FDA may still require studies demonstrating device performance (e.g., analytical evaluations) but generally intends to rely on the scientific literature to support clinical validity if appropriate. FDA intends to work with the laboratory community, the healthcare professional community and other stakeholders to determine whether an LDT's clinical validity has already been established in the literature.

(h) Third Party Review

FDA has an established third party review program for eligible medical devices[38]. For LDTs, FDA envisions that the Agency would generally review PMAs for high-risk (Class III) LDTs, whereas third parties would generally review the 510(k)s for lower risk (Class II) LDTs. FDA seeks to work with interested parties that have experience with laboratories and can meet FDA requirements for third party reviewers. FDA anticipates that inclusion of such groups will facilitate a more efficient review process for LDTs. If this approach is successful, most 510(k)s for LDTs could be reviewed by appropriate third parties.

[38] Further information regarding FDA's current third party review program can be found at: http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/thirdparyreview/default.htm

6. Quality System Regulation Requirements

The Quality System Regulation (21 CFR Part 820) was developed to define the minimal quality system requirements that medical device manufacturers must implement in order to assure that the finished device will be safe and effective. FDA intends to continue to exercise enforcement discretion with respect to QS reg requirements, codified in 21 CFR Part 820, until a manufacturer of a given LDT submits a PMA or FDA issues a 510(k) clearance order for the LDT. Under this enforcement policy, the clinical laboratory manufacturing and using the LDT will be responsible for having a quality system in place that meets the minimum requirements codified in 21 CFR Part 820, either at the time of PMA submission (the facility that makes the device must pass an inspection as a condition of PMA approval as a matter of law (21 CFR 814.45(a)(3))), or prior to market launch for cleared devices, as applicable. This initial period of continued exercise of enforcement discretion for QS reg requirements is intended to allow time for laboratories to learn about their regulatory obligations under the Act, as well as to develop programs to comply with them. FDA intends to assist laboratories in understanding these and other applicable requirements prior to enforcing those requirements.

FDA recognizes that there may currently be low-risk LDTs that, based upon intended use and technology, would be classified as Class I diagnostic devices that are not exempt from 510(k) submission requirements, or Class I or II diagnostic devices that are exempt from 510(k) submission requirements.[39] FDA intends to continue exercising enforcement discretion with respect to QS reg requirements for these LDTs at this time. The Agency intends to provide adequate notice before it begins enforcing QS reg requirements for these LDTs, should it decide to enforce these requirements for these tests in the future.

The Agency encourages laboratories to begin working toward building elements of the QS reg requirements into their practices as these requirements apply to the design and manufacture of LDTs. Specifically, the Agency encourages laboratories developing new LDTs to implement design controls (21 CFR 820.30(a)-(j)). When applied appropriately, the design control elements described by the QS reg ensure a more robust device design with fewer device defects and recalls.

FDA also intends to expand its third party inspection program for surveillance inspections, and to explore opportunities to coordinate with and leverage existing programs, for example, to minimize or avoid additional inspections as a result of implementation of the framework described in this guidance.

[39] The majority of Class I medical devices are exempt from 510(k) premarket notification requirements under current regulations; however, a small number of Class I devices are not exempt and therefore, are subject to 510(k) premarket notification requirements. Conversely, only a small number of Class II devices are exempt from 510(k) premarket notification requirements under the current regulations, and therefore, most Class II devices are subject to 510(k) premarket notification requirements.

APPENDIX A: LDT Oversight Framework Summary

The following table provides a summary of the draft framework for regulatory oversight of LDTs.

Category	Requirements FDA Intends to Enforce			
	Registration and Listing (Section 510) of the FD&C Act; 21 CFR Part 807) where no FDA Notification has been provided by the laboratory	**Manufacturer Reporting Requirements for Medical Device Reporting (Section 519(a) of the FD&C Act; 21 CFR Part 803 Subpart E)**	**Premarket Review Requirements (Sections 510(k) and 515 of the FD&C Act; 21 CFR Part 807, Subpart E; 21 CFR Part 814)**	**Quality System Regulation Requirements (Section 520(f) of the FD&C Act; 21 CFR Part 820)**
LDTs solely used for forensic (law enforcement) purposes LDTs used in CLIA-certified, high-complexity histocompatibility laboratories for transplantation				
LDTs used for Rare Diseases	X	X		
Traditional LDTs	X	X		
LDTs for Unmet Needs	X	X		
LDTs with the same intended use as a cleared or approved Companion Diagnostic LDTs with the same intended use as an approved Class III medical device Certain LDTs used to determine safety/efficacy of blood or blood products	X	X	• Enforced for currently marketed LDTs that have not made a premarket submission within 12 months of finalization of this guidance document • Enforced for new LDTs initially marketed after finalization of this guidance document	• Enforced once PMA submitted or FDA issues clearance order
LDTs for Infectious Agents (donor screening tests) used in blood and blood components and HCT/Ps	• All requirements currently enforced			
Class III (high risk) LDTs	X	X	• Enforced on a risk-based, phased-in basis • FDA plans to announce the priority list within 24 months of finalization of this guidance	• Enforced on a risk-based, phased-in basis until a manufacturer of a given LDT submits a PMA.
Class II (moderate risk) LDTs	X	X	• Enforced on a risk-based, phased-in basis • Enforced after FDA has completed the phase-in of Class III • FDA plans to announce the priority list for class II within 4 years of finalization of this guidance	• Enforced on a risk-based, phased-in basis until FDA issues a 510(k) clearance order for the LDT
Class I (low risk) LDTs	X	X		

APPENDIX B: LDT Oversight Framework; Questions and Answers

Question 1: **I am a laboratory that makes LDTs for rare disease testing that meet the definition of a Humanitarian Use Device, as described in Section D.5.(a) of this document. What are the relevant enforcement policies under the framework for greater regulatory oversight of LDTs?**

Response:

FDA Notification:

FDA intends to continue to exercise enforcement discretion with respect to Registration and Listing requirements (21 CFR Part 807), provided that you notify the FDA that you are manufacturing LDTs and provide basic information regarding each of these LDTs within 6 months of finalization of this guidance document or prior to offering a new LDT for clinical use after that date.

Specific instructions on how you should appropriately notify the FDA regarding LDT manufacture and provide basic information regarding the LDTs are provided in the draft guidance document entitled "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)."

Medical Device Reporting:

FDA intends to continue to enforce the medical device reporting requirements for user facilities (21 CFR Part 803, Subpart C) for all diagnostic tests used in your facility.

If you are a laboratory that makes LDTs (excluding the categories outlined in Section D.2 of this guidance document), FDA intends to enforce the medical device reporting requirements for medical device manufacturers (21 CFR Part 803, Subpart E) beginning 6 months after finalization of this guidance only for those LDTs manufactured by your laboratory.

Further instructions on how you may meet your MDR reporting obligations as both a user facility as well as a medical device manufacturer are provided in the draft guidance document entitled "FDA Notification and

Medical Device Reporting for Laboratory Developed Tests."

Question 2: **I am a laboratory that makes "Traditional LDTs" as described in Section D.5.(a) of this document. There is an equivalent FDA cleared/approved device with the same intended use as my LDT on the market. What are the relevant enforcement policies under the framework for greater regulatory oversight of LDTs?**

Response:

FDA Notification:

FDA intends to continue to exercise enforcement discretion with respect to Registration and Listing requirements (21 CFR Part 807), provided that you notify the FDA that you are manufacturing LDTs and provide basic information regarding each of these LDTs within 6 months of finalization of this guidance document or prior to offering a new LDT for clinical use after that date.

Specific instructions on how you should appropriately notify the FDA regarding LDT manufacture and provide basic information regarding the LDTs are provided in the draft guidance document entitled "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)."

Medical Device Reporting:

FDA intends to continue to enforce the medical device reporting requirements for user facilities (21 CFR Part 803, Subpart C) for all diagnostic tests used in your facility.

If you are a laboratory that makes LDTs (excluding the categories outlined in Section D.2 of this guidance document), FDA intends to enforce the medical device reporting requirements for medical device manufacturers (21 CFR Part 803, Subpart E) beginning 6 months after finalization of this guidance only for those LDTs manufactured by your laboratory.

Further instructions on how you may meet your MDR reporting obligations as both a user facility as well as a medical device manufacturer are provided in the draft guidance document entitled "FDA Notification and

Medical Device Reporting for Laboratory Developed Tests."

Premarket Review Requirements: While FDA has indicated that it intends to enforce premarket review requirements for LDTs that have the same intended use as an FDA cleared/approved device, considering the factors described in Section D.5.(a) of this document, FDA intends to exercise enforcement discretion with respect to medical device premarket requirements for your "Traditional LDTs."

Question 3: I am a laboratory that makes LDTs that have the same intended use as a cleared or approved Companion Diagnostic and/or that have the same intended use as an approved Class III medical device. What are the relevant enforcement policies under the framework for greater regulatory oversight of LDTs?

Response:

FDA Notification: FDA intends to continue to exercise enforcement discretion with respect to Registration and Listing requirements (21 CFR Part 807), provided that you notify the FDA that you are manufacturing LDTs and provide basic information regarding each of these LDTs within 6 months of finalization of this guidance document.

Specific instructions on how you should appropriately notify the FDA regarding LDT manufacture and provide basic information regarding the LDTs are provided in the draft guidance document entitled "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)."

Registration and Listing: If you are a laboratory that is engaged in the manufacture, preparation, propagation, compounding, assembly, or processing of an LDT intended for human use, FDA intends to enforce all applicable registration and listing requirements (21 CFR Part 807) once a premarket submission has been made to the Agency for that LDT.

Medical Device Reporting: FDA intends to continue to enforce the medical device reporting requirements for user facilities (21 CFR Part

803, Subpart C) for all diagnostic tests used in your facility.

If you are a laboratory that makes LDTs (excluding the categories outlined in Section D.2 of this guidance document), FDA intends to enforce the medical device reporting requirements for medical device manufacturers (21 CFR Part 803, Subpart E) beginning 6 months after finalization of this guidance only for those LDTs manufactured by your laboratory.

Further instructions on how you may meet your MDR reporting obligations as both a user facility as well as a medical device manufacturer are provided in the draft guidance document entitled "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)."

Premarket Review Requirements: If you are a laboratory that makes the types of LDTs described in this question, FDA intends to exercise enforcement discretion with respect to premarket submission requirements for these LDTs for 12 months following finalization of this guidance document.

If you are a laboratory that will be manufacturing and using a new LDT (i.e., an LDT initially marketed for use after the date of finalization of this guidance document) that has the same intended use as a cleared or approved companion diagnostic or that has the same intended use as an approved Class III device, you may be subject to enforcement action if you market the device prior to FDA clearance/approval. FDA intends to enforce the premarket requirements (21 CFR Part 807, Subpart E, and 21 CFR Part 814) for these new LDTs.

Quality System Requirements: FDA intends to enforce the QS reg requirements in 21 CFR Part 820 upon submission of a PMA or FDA clearance of a 510(k).

Question 4: I am a laboratory that makes LDTs for Infectious Agents (donor screening tests) used in blood and blood components. What are the relevant enforcement policies under the framework for greater regulatory oversight of LDTs?

Response:

FDA Requirements: FDA intends to continue to enforce all FDA requirements for LDTs in this category.

Question 5: **I am a laboratory that makes LDTs that do not fit into any of the categories described in this document. What are the relevant enforcement policies under the framework for greater regulatory oversight of LDTs?**

Response:

FDA Notification: FDA intends to continue to exercise enforcement discretion with respect to Registration and Listing requirements (21 CFR Part 807), provided that you notify the FDA that you are manufacturing LDTs and provide basic information regarding each of these LDTs within 6 months of finalization of this guidance document or prior to offering a new LDT for clinical use after that date.

Specific instructions on how you should appropriately notify the FDA regarding LDT manufacture and provide basic information regarding the LDTs are provided in the draft guidance document entitled "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)."

Registration and Listing: FDA intends to enforce the registration and listing requirements in a risk-based, phased-in manner. If you are a laboratory that is engaged in the manufacture, preparation, propagation, compounding, assembly, or processing of an LDT intended for human use, FDA intends to enforce all applicable registration and listing requirements (21 CFR Part 807) once a premarket submission has been made to the Agency for that LDT.

Medical Device Reporting: FDA intends to continue to enforce the medical device reporting requirements for user facilities (21 CFR Part 803, Subpart C) for all diagnostic tests used in your facility.

If you are a laboratory making such LDTs, FDA intends to enforce the medical device reporting requirements for medical device manufacturers (21 CFR Part 803, Subpart E) beginning 6 months after

finalization of this guidance only for those LDTs manufactured by your laboratory.

Premarket Review Requirements: FDA intends to enforce premarket review requirements in a risk-based, phased-in manner. The Agency plans to announce its intent to enforce premarket requirements for a given category of LDTs well in advance of implementation. FDA intends to start enforcing premarket requirements for the LDT categories described in Section D.5.(c) of this guidance 12 months after finalization of this guidance; and for all other Class III and Class II LDTs, as described in the priority list for Class III LDTs that FDA intends to announce 24 months after finalization of this guidance and as described in the priority list for Class II LDTs that FDA intends to announce 4 years after finalization of this guidance.

If you are a laboratory that will be manufacturing and using a new LDT in an area where the Agency has begun enforcing premarket requirements under 21 CFR Part 807, Subpart E, and 21 CFR Part 814, you may be subject to enforcement action if you market the device prior to FDA clearance/approval.

Quality System Requirements: FDA intends to enforce the QS reg requirements in 21 CFR Part 820 upon submission of a PMA, or upon premarket clearance, as applicable.

Question 6: I am a principal investigator developing a new LDT in a lab at an academic medical center. What are the relevant requirements for compliance with FDA's investigational device exemption regulation and what are the relevant enforcement policies under the framework for greater regulatory oversight of LDTs?

Response:

The regulatory requirements for investigational devices are the same for academic medical center investigators as for other investigators. Investigational IVDs, including LDTs, are reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions that are the object of an investigation, and are subject to the Investigational Device Exemption (IDE) regulation (21 CFR Part 812), which is intended to protect the safety of study subjects. Unless exempted under 21 CFR 812.2, an approved IDE is required

to allow the shipment of investigational IVDs and their use in investigations.[40] The vast majority of IVD development programs involve IVD studies that are defined as "exempted investigations" under 21 CFR 812.2. However, if the device is non-exempt (e.g., if invasive sampling is performed to obtain the specimen in a way that may pose significant risk to patients, or if test results are returned to patients without confirmation by a medically accepted diagnostic product or procedure), the IDE regulation requirements apply. For general information on IDEs, see Guidance on IDE Policies and Procedures, at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm, or if you would like to discuss specific questions with FDA through the Pre-submission program regarding IVD development or application preparation, see FDA guidance "The Pre-Submission Program and Meetings with Food and Drug Administration Staff", found at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.

As with other LDT manufacturers, when an academic medical center offers an LDT for clinical use, the following are the relevant enforcement policies:

FDA Notification:

FDA intends to continue to exercise enforcement discretion with respect to Registration and Listing requirements (21 CFR Part 807), provided that you notify the FDA that you are manufacturing LDTs and provide basic information regarding each of these LDTs within 6 months of finalization of this guidance document or prior to offering a new LDT for clinical use after that date.

Specific instructions on how you should appropriately notify the FDA regarding LDT manufacture and provide basic information regarding the LDTs are provided in the draft guidance document entitled "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)."

Registration and Listing:

FDA intends to enforce the registration and listing requirements in a risk-based, phased-in manner. If you are a laboratory that is engaged in the manufacture, preparation, propagation, compounding, assembly, or processing of an LDT intended for human use, FDA intends to enforce all applicable registration and listing requirements (21 CFR Part 807) once a premarket submission has been made to the Agency for that LDT.

[40] Investigations of significant risk devices, as defined in 21 CFR 812.3(m), require FDA approval of an IDE application. Investigations of nonsignificant risk devices that meet the conditions described in 21 CFR 812.2(b) are considered to have an approved IDE without FDA review and approval of an application.

Medical Device Reporting:	FDA intends to continue to enforce the medical device reporting requirements for user facilities (21 CFR Part 803, Subpart C) for all diagnostic tests used in your facility. If you are a laboratory making such LDTs, FDA intends to enforce the medical device reporting requirements for medical device manufacturers (21 CFR Part 803, Subpart E) beginning 6 months after finalization of this guidance only for those LDTs manufactured by your laboratory.
Premarket Review Requirements:	FDA intends to enforce premarket review requirements in a risk-based, phased-in manner. The Agency plans to announce its intent to enforce premarket requirements for a given category of LDTs well in advance of implementation. FDA intends to start enforcing premarket requirements for the LDT categories described in Section D.5.(c) of this guidance 12 months after finalization of this guidance; and for all other Class III and Class II LDTs, as described in the priority list for Class III LDTs that FDA intends to announce 24 months after finalization of this guidance and as described in the priority list for Class II LDTs that FDA intends to announce 4 years after finalization of this guidance. If you are a laboratory that will be manufacturing and using a new LDT in an area where the Agency has begun enforcing premarket requirements under 21 CFR Part 807, Subpart E, and 21 CFR Part 814, you may be subject to enforcement action if you market the device prior to FDA clearance/approval.
Quality System Requirements:	FDA intends to enforce the QS reg requirements in 21 CFR Part 820 upon submission of a PMA, or upon premarket clearance, as applicable.

APPENDIX C: Regulatory Resources for LDTs

1. Registration and Listing

Applicable Laws and Regulations: Section 510 of the FD&C Act (21 U.S.C. 360); 21 CFR Part 807

Applicable Resources:

- "Implementation of Medical Device Establishment Registration and Device Listing Requirements Established by the Food and Drug Administration Amendments Act of 2007" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm185871.htm)
- Device Advice: Registration and Listing (http://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/registrationandlisting/default.htm)

2. Medical Device Reporting

Applicable Laws and Regulations: Sections 519(a),(b), and (c) of the FD&C Act (21 U.S.C. 360i); 21 CFR Part 803

Applicable Resources:

- Device Advice: Reporting Adverse Events (Medical Devices) (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/default.htm)

3. Medical Device Corrections and Removals

Applicable Laws and Regulations: Section 519 of the FD&C Act (21 U.S.C. 360i); 21 CFR Part 806

Applicable Resources:

- Device Advice: Recalls Corrections and Removals (Devices) (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/RecallsCorrectionsAndRemovals/default.htm)

4. Quality System Regulation

Applicable Laws and Regulations: Section 520(f) of the FD&C Act (21 U.S.C. 360j); 21 CFR Part 820

5. Labeling

Applicable Laws and Regulations: Section 502 of the Act (21 U.S.C. 352); 21 CFR Part 809

Applicable Resources:

- Device Advice: In Vitro Diagnostic Device Labeling Requirements (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/InVitroDiagnosticDeviceLabelingRequirements/default.htm)

6. Premarket Requirements

Applicable Laws and Regulations: Sections 510, 513, and 515 of the FD&C Act (21 U.S.C. 360, 360c, and 360e); 21 CFR Part 807, Subpart E, and 21 CFR Part 814; Section 351 of the Public Health Service Act; 21 CFR Parts 600-680

Applicable Resources:

General Device Requirement Resources

- Device Advice: How to Market Your Device (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/default.htm)
- CDRH LEARN (http://www.fda.gov/Training/CDRHLearn/default.htm)
- CDRH Sponsored Workshops, Training Conferences and Other Meetings (http://www.fda.gov/http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/default.htmMedicalDevices/NewsEvents/WorkshopsConferences/default.htm)

Resources Associated with Modifications to Devices

- "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm)
- "Deciding When to Submit a 510(k) for a Change to an Existing Device" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm)
- "30-Day Notices and 135-Day PMA Supplements for Manufacturing Method or Process Changes, Guidance for Industry and CDRH" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080192.htm)

IDE and Investigational Studies for IVDs Resources:

- Guidance on Informed Consent for *In Vitro* Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable (http://www.fdahttp://www.fda.gov/MedicalDevices/DeviceRegulationandGui

dance/GuidanceDocuments/ucm078384.htm.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm078384.htm)

- In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071230.pdf)

For the Purpose of Notification to Congress Only

Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

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FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)

This document provides the anticipated details of the *Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)* that FDA intends to issue in 60 days, and is being provided to Congress pursuant to section 1143 of the Food and Drug Administration Safety and Innovation Act of 2012

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of *In Vitro* Diagnostics and Radiological Health

Center for Biologics Evaluation and Research

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Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

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FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)

A. Introduction

This document is intended to describe the process for clinical laboratories to notify the FDA of the laboratory developed tests (LDTs) they manufacture as well as to describe the Medical Device Reporting (MDR) requirements, codified in 21 CFR Part 803, for clinical laboratories manufacturing LDTs. LDTs are those *in vitro* diagnostic devices (IVD) that are intended for clinical use and are designed, manufactured and used within a single laboratory.[1, 2]

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

B. Background

LDT Background and Regulatory History

In 1976, Congress enacted the Medical Device Amendments (MDA), which amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) to create a comprehensive

[1] Single laboratory refers to a facility with a single CLIA certificate as described in 42 CFR 493.43(a)-(b). (See also 42 CFR 493.55). LDTs should only be designed, manufactured, and used by laboratories that meet the requirements for high-complexity testing under CLIA as described in 42 CFR 493.17(c)(4) and 493.25.

[2] The scope of this guidance is consistent with the scope of the Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs).

system for the regulation of medical devices intended for use in humans. At that time, the definition of a device was amended to make explicit that it encompasses *in vitro* diagnostic devices (IVDs).[3] The definition of device applies equally to *in vitro* diagnostics manufactured by conventional device manufacturers and those manufactured by laboratories. An IVD, therefore, meets the device definition irrespective of where and by whom it is manufactured.

However, since the implementation of the MDA of 1976, FDA has generally exercised enforcement discretion so that the Agency has generally not enforced applicable provisions under the FD&C Act and FDA regulations with respect to LDTs.

Since 1976, when Congress clarified that IVDs were medical devices under the FD&C Act and FDA opted to exercise enforcement discretion with respect to LDTs under this authority, the industry has grown and evolved in significant ways. FDA now finds that in the absence of appropriate oversight of LDTs, there is the potential for increased risk for patients. FDA recognizes that, as with all IVDs, potential risks vary with the wide variety of LDTs. Thus, FDA believes that a risk-based approach to regulatory oversight of LDTs is appropriate and necessary to protect patient safety.

Consistent with the draft guidance entitled "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" (LDT Framework Guidance Document) that is being distributed for comment in coordination with this document, FDA intends to enforce certain device requirements for LDTs and device manufacturer requirements for laboratories that manufacture, prepare, propagate, compound, assemble or process LDTs.[4] FDA intends to collect information regarding LDTs currently being offered for clinical use through a notification process. In addition, FDA intends to enforce the requirements under 21 CFR Part 803 for reporting safety issues related to LDTs to provide a mechanism for collecting information on any known or suspected adverse events related to the use of an LDT. The FDA believes that this is the appropriate regulatory approach to adopt to achieve the desired public health goal of assuring that these IVD tests used in the provision of health care, regardless of the manufacturer, provide reasonable assurance of safety and effectiveness.

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[3] Section 201(h) of the FD&C Act provides:
(h) The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is--
(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

[4] See 21 CFR 807.3(d) for definition of these terms. This guidance document uses "manufacture" to encompass all of these terms.

C. Scope

The goal of this document is to explain to clinical laboratories how they should appropriately notify the FDA of all of the LDTs manufactured, prepared, propagated, compounded, or processed by their laboratories. This guidance also provides information about how to comply with FDA's MDR requirements as they apply to LDTs.

D. Notification to FDA of all LDTs Manufactured by a Laboratory

The notification process described below is intended to collect information on the LDTs being used by laboratories in order to classify LDTs by risk level and assist FDA in determining its priorities in enforcing premarket review requirements for different types of LDTs.

The specific information that should be provided with each LDT notification is described in Appendix A of this document. Information should be submitted on-line through the FDA website. Notification is expected to occur once for each LDT, although if significant changes are made to an LDT, additional notification should be provided.

Completion of this notification does not constitute compliance with registration and listing requirements, nor will the laboratory be considered to be registered and listed with the FDA.

Notification Process for LDTs Currently on the Market and New LDTs on the Market within 6 Months after Publication of the Final LDT Framework Guidance Document:
For all LDTs on the market on the date of publication of the final version of the LDT Framework Guidance Document, and new LDTs that come on the market for the following 6 months after publication of the document, FDA intends to continue to exercise enforcement discretion with respect to the registration and listing requirements, as described in 21 CFR Part 807, for owners and operators of laboratories[5] that manufacture, prepare, propagate, compound, assemble, or process[6] LDTs, provided that these laboratory owners/operators notify the Agency and provide basic information regarding all of the LDTs they manufacture within 6 months of publication of the final LDT Framework Guidance Document.

Notification for New LDTs on the Market after the 6-month Period following Publication of the Final LDT Framework Guidance Document:

[5] Laboratory refers to a facility with a single CLIA certificate as described in 42 CFR 493.43(a)-(b). (See also 42 CFR 493.55).
[6] See 21 CFR 807.3(d) for definition of these terms. This guidance document uses "manufacture" to encompass all of these terms.

Starting 6 months after publication of the final version of the LDT Framework Guidance Document, FDA intends to continue to exercise enforcement discretion with respect to the registration and listing requirements, as described in 21 CFR Part 807, for owners and operators of laboratories[7] that manufacture, prepare, propagate, compound, assemble, or process[8] new LDTs, provided that these laboratory owners/operators notify the Agency and provide basic information regarding the new LDTs they manufacture prior to offering these LDTs for clinical use.

Notification to FDA regarding Significant Changes to LDTs:
When a laboratory makes a significant change to the marketed intended use of an LDT for which they have previously provided notification, the LDT will be considered by the FDA to be a new LDT.[9] Therefore, a new notification should be provided within 6 months of publication of the final LDT Framework Guidance Document or prior to offering that LDT for clinical use if offered after that 6-month period. This notification is especially important for those changes in marketed intended use that increase the risk of the device. Additionally, FDA urges laboratories that make other significant modifications to LDTs after the initial notification to re-submit notification data to FDA to communicate such changes (see section D.5.(e) of the LDT Framework Guidance Document for additional information on significant device modifications).

Laboratories That Do Not Provide Notification:
Laboratories that do not opt to notify the Agency and provide basic information regarding each of the LDTs manufactured in their laboratory within the abovementioned timeframes or that do not opt to notify the Agency and provide basic information after a significant change is made to the marketed intended use of their LDT will not be within the scope of FDA's enforcement discretion policy with respect to the registration and listing requirements codified in 21 CFR Part 807. Such laboratories would fall within the agency's normal enforcement approach with respect to the registration and listing requirements. These requirements include payment of the required registration fee (Section 738(a)(3) of the FD&C Act; 21 U.S.C. 379j(a)(3)), registration of each establishment[10] with the FDA, and listing of the devices manufactured in these facilities (21 CFR 807.20(a)).

Instructions for Establishments That Are Involved in the Manufacture of Other Medical Devices, in Addition to LDTs:
FDA intends to exercise enforcement discretion with respect to registration and listing requirements solely for laboratories that manufacture prepare, propagate, compound, assemble, or process *only* LDTs. Establishments that manufacture, prepare, propagate, compound, assemble, or process other medical devices, in addition to LDTs, must comply with the registration and listing requirements codified in 21 CFR Part 807,

[7] *See supra* note 3.
[8] *See supra* note 4.
[9] For purposes of this guidance, FDA uses the term "marketed intended use" to refer to the use(s) of a test that a laboratory promotes or includes in any applicable labeling. Although FDA generally considers new devices to include other types of modifications to an existing device (e.g., technological changes), for the purposes of this subsection only, new LDTs do not include other types of modifications to an existing LDT.
[10] See 21 CFR 807.3(c) for definition of "establishment."

including payment of the required registration fee (Section 738(a)(3) of the FD&C Act; 21 U.S.C. 379j(a)(3)), registration of their establishment with the FDA and listing of the devices manufactured in these facilities (21 CFR 807.20(a)), including LDTs. FDA does not believe that enforcement discretion is warranted for such laboratories because FDA is already enforcing registration and listing requirements for such establishments based upon their activities related to other medical device products.

When completing registration and listing with the FDA, owners and operators of these establishments should provide listing information for their LDT by utilizing the LDT product code, "OQS" into the FDA's Unified Registration and Listing System (FURLS). This product code is specific for LDTs that have not received product codes through the FDA clearance or approval process.

Registration and Listing Requirements for LDTs that Seek FDA Clearance or Approval

FDA intends to enforce registration and listing requirements for establishments that manufacture, prepare, propagate, compound, assemble or process an LDT once a laboratory has submitted a premarket submission (e.g., premarket approval application or a premarket notification submission (510(k))) to the Agency for the LDT. A laboratory may seek premarket clearance/approval for its LDT either because FDA has announced its intent to enforce premarket review requirements for that LDT category (see draft LDT Framework Guidance Document) or because the laboratory has chosen to do so.

Manufacturers of LDTs that receive FDA clearance or approval **should not** list these cleared or approved medical device(s) under the "OQS" product code. Rather, the establishment should utilize the product code that FDA assigns to their medical device in the clearance/approval of their premarket submission. These manufacturers should only use the "OQS" code when listing LDTs that are not cleared or approved.

E. Medical Device Reporting for LDTs

Overview of Medical Device Reporting (MDR) Requirements

Medical Device Reporting (MDR) requirements are codified in 21 CFR Part 803. One objective of the MDR regulation is to provide a mechanism for FDA and device manufacturers to identify and monitor significant adverse events involving medical devices so that problems may be detected and corrected in a timely manner. This regulation implements reporting requirements for importers, manufacturers, and user facilities.

Laboratories have always been subject to certain provisions of the MDR regulation in their capacity as device user facilities[11] (21 CFR 803.10(a), 803.30, 803.32, and 803.33).

[11] A "device user facility" is defined under 21 CFR Part 803.3 as a "hospital, ambulatory surgical facility, nursing home, outpatient diagnostic facility, or outpatient treatment facility. . ." The focus of this guidance document is laboratories offering LDTs.

User facilities are required to report to the device manufacturer, if known, and to FDA no more than 10 work days after the day they become aware of information from any source that reasonably suggests that a device has caused or may have caused or contributed to the death of a patient of their facility. 21 CFR 803.30(a)(1). User facilities are required to submit a report to the device manufacturer[12] no later than 10 work days after the day they become aware of information from any source that a device has or may have caused or contributed to a serious injury to a patient of their facility. 21 CFR 803.30(a)(2). If the device manufacturer is not known, user facilities must report to FDA. 21 CFR 803.30(a)(2). User facilities are also required to submit annual reports (see 21 CFR 803.33) to FDA that include information for each reportable event that occurred during the annual reporting period.

In addition to enforcing laboratories' obligations to report adverse events as user facilities, FDA also intends to enforce manufacturer reporting requirements for laboratories that manufacture[13] LDTs in accordance with 21 CFR Part 803, including 21 CFR 803.10(c), 21 CFR 803.50, and 21 CFR 803.52. The following guidance is intended to assist clinical laboratories in submitting adverse event reports as manufacturers and to meet their other requirements as manufacturers under 21 CFR Part 803, including 21 CFR 803.17, 21 CFR 803.18, 21 CFR 803.53 and 21 CFR 803.56:

1. Manufacturer Reporting Requirements

The MDR regulation requires the manufacturer of a medical device to submit reports to the FDA whenever they become aware[14] of information that reasonably suggests that a device they market may have caused or contributed to[15] a death or serious injury[16], or has malfunctioned and the malfunction would be likely to cause or contribute to a reportable death or serious injury should it recur. 21 CFR 803.50.

Manufacturers (21 CFR 803.3), including foreign manufacturers, of medical devices are required to:

- Submit MDR reportable events involving their medical devices as described in 21 CFR 803.10(c), 21 CFR 803.50, and 21 CFR 803.52;

[12] Note that, for LDTs, the laboratory is both the user facility and the manufacturer.

[13] In accordance with 21 CFR 803.3 a manufacturer is "any person who manufactures, prepares, propagates, compounds, assembles, or processes a device by chemical, physical, biological or other procedure." This definition therefore encompasses laboratories that design and manufacture LDTs, or those that significantly modify FDA cleared/approved devices (e.g., modify performance or intended use).

[14] A manufacturer has "become aware" of an event when an employee of the entity required to report has acquired information to reasonably suggest a reportable adverse event has occurred. (21 CFR 803.3).

[15] The term "caused or contributed to" means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, malfunction, improper or inadequate design, manufacture, labeling, or user error. (21 CFR 803.3)

[16] "Serious Injury" means an injury or illness that is life-threatening, results in permanent impairment of a body function or permanent damage to a body structure, or necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. (21 CFR 803.3)

- Submit 5-day reports as described in 21 CFR 803.53;
- Submit supplemental reports as described in 21 CFR 803.56;
- Conduct an investigation of each event and evaluate the cause of the event as described in 21 CFR 803.50(b)(3);
- Develop, maintain, and implement written MDR procedures described in 21 CFR 803.17; and
- Establish and maintain complete files for all MDR events concerning adverse medical device events as described in 21 CFR 803.18(a) and (e).

When to submit a report

All clinical laboratories manufacturing LDTs for clinical use are required as medical device manufacturers to submit MDR reports to the FDA as follows:

- Submit reports of individual adverse events no later than 30 calendar days after the day that the laboratory becomes aware of information from any source, that reasonably suggests that an LDT they manufacture:
  - May have caused or contributed to a death or serious injury or
  - Has malfunctioned and this device or similar LDT they manufacture would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur. (21 CFR 803.50(a))
- Submit reports of individual adverse events no later than 5 working days after the day that the laboratory becomes aware of a reportable event that necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health; or a reportable event for which the FDA has made a written request. (21 CFR 803.53)
- Submit supplemental reports within 1 month of the day the laboratory receives reportable information that was not submitted in an initial report. (21 CFR 803.56)

How to submit a report

Laboratories reporting on adverse events related to their LDTs must complete the MedWatch 3500A form available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf then mail the completed form to FDA.[17]

Submit MedWatch 3500A forms to:

[17] The MDR regulation in 21 CFR Part 803 was amended on February 14, 2014, to require device manufacturers and importers to submit MDRs (including supplemental reports) to the FDA in electronic format as specified in the amended rule. 79 FR 8832. The amended rule takes effect on August 14, 2015. *Id*. Once the amended rule takes effect, LDT manufacturers must submit MDRs (including supplemental reports) to the FDA in electronic format as specified in the amended rule unless FDA grants an exemption under 21 CFR 803.19. *Id*.

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, MD 20847-3002

These forms can also be submitted electronically. For electronic filing instructions please see Section E, question 14.

Please note: Laboratories that have not registered and listed with the FDA, but that have notified the FDA of their LDTs using the process described in the guidance should utilize their notification confirmation number, instead of a FDA registration number, to create an appropriate "Mfr Report Number" (top right hand corner of MedWatch 3500A form).

Additionally, laboratories should include the term "procode OQS" (unless the LDT has been cleared or approved by FDA, in which case the procode assigned in the clearance/approval process should be used) in the section of the MedWatch 3500A form entitled "D. Suspect Medical Device" subsection D.4 "Other."

The MDR report (MedWatch 3500A form) must contain all the information described in 21 CFR 803.52 that is known or reasonably known to the clinical laboratory as a manufacturer. Information reasonably known includes any information that:

- Can be obtained by contacting a user facility, importer, or other initial reporter;
- Is in the possession of the manufacturer; or
- Can be obtained by analysis, testing, or other evaluation of the device.

21 CFR 803.50(b).

Instructions for completing specific items on the MedWatch 3500A form can be found at: http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf.

The coding manual can be found at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm106737.htm.

2. Requirement for developing, maintaining and implementing written MDR procedures

As is the case with other medical device manufacturers, clinical laboratories manufacturing LDTs for clinical use must develop, maintain, and implement written MDR procedures. 21 CFR 803.17. Specifically, these procedures should include internal systems that provide instructions for: timely and effective identification, communication,

and evaluation of events that may be subject to MDR requirements; a standardized review process or procedure that assists in determining when an event meets MDR reporting criteria; and timely transmission of complete MDR reports to the FDA. 21 CFR 803.17(a).

Further, these procedures must include instructions for how the clinical laboratory will address documentation and record keeping requirements for: information that was evaluated to determine if an event was reportable; all medical device reports and information submitted to the FDA; any information that was evaluated for the purpose of preparing the submission of annual reports; and systems that ensure access to information that facilitates timely follow-up and inspection by FDA. 21 CFR 803.17(b).

Laboratories, as manufacturers, are also required to establish and maintain MDR event files, required by 21 CFR 803.18.

For additional guidance on the MDR regulation and the reporting requirements, refer to the document titled "Medical Device Reporting for Manufacturers" at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094529.htm.

Reporting Adverse Events as a User Facility and as a Manufacturer

1. What are the basic adverse event reporting obligations for user facilities and manufacturers?

A. Reports of individual adverse events required for user facilities and manufacturers under 21 CFR Part 803:

User facilities and manufacturers report individual adverse events to FDA under a uniform, unified reporting system. Both user facilities and manufacturers report adverse events on the same MedWatch 3500A form, the "Medication and Device Experience Report." 21 CFR 803.11 (You can find a copy of the Mandatory MedWatch report form at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf).

When a user facility receives information about a reportable adverse event, it must report the event to FDA and/or the manufacturer after it becomes aware of the adverse event. 21 CFR 803.30. The user facility fills out certain parts of the MedWatch 3500A form and forwards copies of the form to both FDA and the manufacturer within ten (10) work days after the day the user facility becomes aware if the adverse event involves a death. If the adverse event involves a serious injury, the user facility is required to report the event to the manufacturer within ten (10) work days after the day the user facility becomes aware of the event. 21 CFR 803.30. If the identity of the manufacturer is unknown, the user facility must report the

serious injury to FDA within ten (10) work days after the day the user facility becomes aware of the event. 21 CFR 803.30.

The manufacturer, after becoming aware of the reportable event from the user facility, further investigates the event and provides additional information on the MedWatch 3500A form. 21 CFR 803.50. The manufacturer must submit a completed MedWatch 3500A form to FDA within thirty (30) calendar days after the day it becomes aware of the adverse event. 21 CFR 803.50. A manufacturer also is obligated to submit a MedWatch 3500A form to FDA within five (5) work days after the day it becomes aware of a reportable MDR event that requires remedial action in accordance with 21 CFR 803.53. This requirement is further discussed in question 6D, below. 21 CFR Part 803, Subpart E.

B. Other adverse event reports required for user facilities:

User facilities must complete and submit to FDA an annual report by January 1 of each year. 21 CFR 803.33. Under 21 CFR 803.33, the information in the annual report must include:

- User facility's Center for Medicare and Medicaid Services (CMS) provider number or the number assigned by FDA for reporting purposes;
- Reporting year;
- Facility name and complete address;
- Total number of reports attached or summarized;
- Date of the annual report and the lowest and highest user facility report number of medical device reports submitted during the report period (for example, 123456790-2001-0001 through 0895);
- Name, position title, and complete address of the user facility contact person responsible for reporting to us and whether that person is a new contact for you; and
- Information for each reportable event that occurred during the annual reporting period (see 21 CFR 803.33 (7) (i-vi) for details).

The annual report information must be submitted to the Agency using FDA form 3419 or its electronic equivalent as approved by FDA under 21 CFR 803.14. 21 CFR 803.33. If no reports are submitted to either FDA or manufacturers during these time periods, no annual report is required. 21 CFR 803.33(c).

C. Other adverse event reports required for manufacturers:

Manufacturers are required to submit Supplemental Reports of required information that was not known or was not available at the time of the initial report. 21 CFR 803.56. This information must be submitted within one (1) month of the day the manufacturer receives the information. 21 CFR 803.56.

2. How does being a manufacturer of a device change my adverse event reporting obligations?

As an entity that is a manufacturer of a device in addition to being a user facility, your clinical laboratory is now also subject to the manufacturer's adverse event reporting requirements. **Accordingly, for adverse events involving LDTs, you must fulfill both the 21 CFR Part 803 reporting requirements of a user facility and a manufacturer.** 21 CFR 803.3. This guidance document is intended to assist you in determining when a clinical laboratory must fulfill both the user facility and the manufacturer reporting requirements of 21 CFR Part 803 and when you only have to fulfill the user facility reporting requirements of 21 CFR Part 803.

3. What are the major differences between the user facility and manufacturer adverse event reporting requirements under 21 CFR Part 803?

There are several significant differences between reporting an adverse event to FDA as a user facility versus as a device manufacturer. Device manufacturers are required to report serious injuries to FDA rather than to the manufacturer; fill out additional sections of MedWatch 3500A form; report certain device malfunctions; and submit five (5) day remedial action event reports to the Agency. In addition to filing the MedWatch 3500A form, manufacturers are required to submit Supplemental MDR Reports as appropriate.

4. How do I know if I am required to report as a manufacturer or a user facility?

Whether you are required to fulfill the user facility adverse event reporting requirements only, or the manufacturer reporting requirements and the user facility requirements depends on whether the adverse event involved an LDT. The answer to whether you report solely as a user facility or whether you also must report as a manufacturer depends on your answer to the following questions:

A. Does the reportable event involve an LDT that was manufactured by your laboratory?

If the reportable event involved an LDT that your facility manufactured, even if the LDT in question contained critical components, such as Analyte specific reagents (ASRs), that were not manufactured by your laboratory (e.g. FDA cleared/approved devices that have been modified by your laboratory in a way that affects intended use or IVD performance), then you have to fulfill the reporting requirements of a manufacturer and a user facility. 21 CFR 803.3.

B. Does the reportable event involve an IVD or other medical device that was not an LDT manufactured by your laboratory?

If the reportable event involved an IVD or other medical device that was not an LDT that you manufactured, you only have to fulfill the reporting requirements of a user facility. 21 CFR 803.3.

5. What types of adverse events must I report when the event *is not related* to an LDT manufactured by my clinical laboratory?

You are required to fulfill user facility adverse event reporting requirements for:

A. Deaths:
As a user facility, you are obligated to report adverse events to FDA, and to the manufacturer, if known, within ten (10) work days after the day you become aware of information that reasonably suggests that a device has or may have caused or contributed to the death of a patient of your facility. 21 CFR 803.30(a)(1).

B. Serious Injuries:
As a user facility, you are obligated to report adverse events to the manufacturer, or to FDA if the identity of the manufacturer is not known, within ten (10) work days after the day you become aware of information that reasonably suggests that a device has or may have caused or contributed to a serious injury to a patient of your facility. 21 CFR 803.30(a)(2).

6. What types of events must I report as a manufacturer when the event is related to an LDT manufactured by my clinical laboratory?

LDTs are medical devices under the FD&C Act (Section 201(h) of the FD&C Act; 21 U.S.C. 321(h)); therefore, a clinical laboratory that manufactures and offers an LDT for clinical use is considered to be a manufacturer of a medical device. As such, the clinical laboratory must fulfill the manufacturer reporting requirements under 21 CFR 803:

A. Deaths:

As the LDT manufacturer, you are obligated to report adverse events to FDA within thirty (30) calendar days after the day you become aware of information that reasonably suggests that an LDT manufactured by your clinical laboratory has or may have caused or contributed to the death. 21 CFR 803.50(a)(1).

B. Serious Injuries:

As an LDT manufacturer, you are obligated to report adverse events to FDA within thirty (30) calendar days after the day you become aware of information that reasonably suggests that an LDT manufactured by your clinical laboratory has or may have caused or contributed to a serious injury. 21 CFR 803.50(a)(1).

C. Malfunctions:

As an LDT manufacturer, you are obligated to report adverse events to FDA within thirty (30) calendar days after the day you become aware of information that reasonably suggests that the LDT manufactured by your clinical laboratory has

malfunctioned and such device (LDT) or similar device (LDT) also manufactured by your clinical laboratory would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur. 21 CFR 803.50(a)(2).

D. Remedial actions; requests:

As an LDT manufacturer, you are obligated to report adverse events to FDA within five (5) work days after the day you become aware of:

1. a reportable event(s) that necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health, or

2. a reportable event(s) for which FDA has made a written request.

21 CFR 803.53(a) and (b).

7. As an LDT manufacturer, I am obligated to report deaths to FDA within 30 calendar days (see question 6A, above). However, as a user facility, I am obligated to report deaths to FDA within 10 work days (See question 5A, above). Do I complete two separate MedWatch 3500A forms in order to meet the different reporting obligations for the same event?

To avoid filing the same event twice when the event involves a reportable death, you may complete all medical device sections (skip section C) of the MedWatch 3500A form and submit the completed form to the Agency within ten (10) work days.

As the user facility, you must complete sections A – F (skip section C) of the MedWatch 3500A form. 21 CFR 803.32. As the LDT manufacturer, you must complete sections A, B, D, E, G, and H of the MedWatch 3500A form. 21 CFR 803.52. Thus, as both, you must complete sections A, B, and D-H of the MedWatch 3500A form. 21 CFR 803.32 and 21 CFR 803.52.

8. What is the definition of "Serious Injury"?

"Serious injury" is defined as an injury or illness that:

- is life-threatening;
- results in permanent impairment of a body function or permanent damage to body structure; or
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. 21 CFR 803.3.

9. What is the definition of "Malfunction"?

"Malfunction" is defined as the failure of a device to meet its performance specifications or otherwise perform as intended. 21 CFR 803.3. Performance specifications include all claims made in the labeling for the device. 21 CFR 803.3. The intended performance of a device refers to the intended use for which the device is labeled or marketed. 21 CFR 801.4 and 21 CFR 803.3.

10. As a user facility, which sections of the MedWatch 3500A form must I complete for a reportable adverse event?

A. On the upper right-hand corner on the front page of the MedWatch 3500A form, enter your user facility number under *UF/Dist report #*. The UF # is a combination of your organization's CMS number (or a number FDA assigned to your organization), the 4-digit calendar year in which the report is submitted, and a 4-digit sequence number of the report submitted during the year (e.g., 1234567890-2011-0001, 1234567890-2011-0002, etc.).

B. Complete all items in section *A. Patient information*.

C. Complete all items in section *B. Adverse event or product problem*.

(Note: skip section *C. Suspect medication(s)*.)

D. Complete all items in section *D. Suspect medical device*. Note that specific device identification information should be entered exactly as it appears on the device or on the device labeling.

E. Complete all items in section *E. Initial reporter*. The initial reporter is the person who provided the information about the adverse event to the user facility.

F. Complete all items in section *F. For use by user facility/distributor- devices only*.

21 CFR 803.20 and 21 CFR 803.32.

11. As the manufacturer, which sections of the MedWatch 3500A form must I complete for a reportable adverse event that *involves an LDT that my clinical laboratory manufactured*?

A. On the upper right-hand corner on the front page of the MedWatch 3500A form, enter your *Mfr. report #*. The *mfr. report #* is composed of either the registration number that FDA assigned to your laboratory when you registered and listed with the Agency as a manufacturer, or the notification confirmation number that you were assigned upon notifying the Agency of your LDTs, the 4-digit calendar year in which the report is submitted, and the 5-digit sequence number for each report submitted during the year (e.g., 9876543210-2011-00001, 9876543210-2011-00002, etc.). You also must enter your user facility report number under *UF/Dist report #* of the MedWatch 3500A form (see 10A above).

B. Complete all items in section *A. Patient information*.

C. Complete all items in section *B. Adverse event or product problem*.

(Note: skip section *C. Suspect medications(s)*.)

D. Complete all items in section *D. Suspect medical device*. For item *D.3. Manufacturer name and address*, enter the name and address of the laboratory that manufactures the LDT. For item *D.4 Other #* enter ”Procode OQS” if your LDT is not approved or cleared by the FDA. If your LDT is approved or cleared by the FDA, please enter “Procode” and then the product-specific procode that was assigned to your device.

E. Complete all items in section *E. Initial reporter*. The initial reporter is the person who provided the information about the adverse event to the user facility or manufacturer.

F. Section *F. For use by user facility/distributor-devices only*. If you are considered to be both the user facility and the manufacturer for the event, then you should fill out this section as the user facility. For malfunction events not submitted by the user facility, the manufacturer’s submission should not include section F of the MedWatch 3500A form. Corrected or missing information for Section F, including relevant patient problem and device problem codes, should be included in the Section H.11 (*Corrected Data*) section of the MedWatch 3500A form provided by the manufacturer.

1. *F.13. Report sent to manufacturer?* The term "manufacturer" in this block refers to the LDT manufacturer.

2. *F.14: Manufacturer name/address*. The term "manufacturer" in this block refers to the LDT manufacturer. Because this information should also be entered in section G.1 *Contact office – name/address (& manufacturing site for devices)*, you may enter in section F.14 *Manufacturer name/address*, "see G.1."

G. Complete all items in section *G. All manufacturers*.

1. *G.1: Contact office – name/address (& manufacturing site for devices).* Information in this block refers to the LDT manufacturer; therefore, enter the contact office, name, and address of the laboratory that is submitting the report of the LDT event.
2. *G.4: Date received by manufacturer (mo/day/yyyy).* This is the date that the laboratory became aware of the adverse event.
3. *G.5, 6, and 8*. These blocks are not applicable to medical devices.

4. *G.7: Type of report*. Only three (3) report types are applicable to LDT manufacturers: *5-day, Initial (i.e., 30-day reports),* and *Follow-up*. Select the report type that is applicable to the event that you are reporting.
5. *G9*: *Manufacturer Report Number*. G9 should match the manufacturer report number that you assigned to the event in the upper right hand corner of your MedWatch 3500A form, and should appear on any additional pages you might attach to the MedWatch 3500A form.

H. Complete all blocks in section *H. Device manufacturers only*. As the LDT manufacturer, you must complete all sections regardless of where the device analysis was performed.
   1. *H.4: Device manufacturing date (mo/yyyy)*. For the purpose of this block, the manufacturing date is the date that the LDT was manufactured by your clinical laboratory. Note: in cases where components of the LDT were manufactured on different dates, FDA considers the "device manufacturing date" to be the date the last component of the LDT was manufactured by the laboratory and/or qualified as suitable for use.

   2. *H.7: If remedial action initiated, check type*. Select the most appropriate remedial action(s) that apply. Under the MDR regulation a "remedial action" is any action, other than routine maintenance or servicing of a device, necessary to prevent recurrence of an MDR reportable event. 21 CFR 803.3. FDA does not consider an action taken to correct only a single device involved in a specific MDR reportable event to be a remedial action.
   21 CFR 803.20, 21 CFR 803.32, and 21 CFR 803.52.

12. When do I have to file reports of corrections and removals?

Under 21 CFR Part 806, you are required to submit a written report to FDA within ten (10) work days of initiating a correction or removal action that was taken:

- to reduce a risk to health posed by the device; or
- to remedy a device problem which may present a risk to health

The Reports of Correction and Removal regulation, 21 CFR Part 806, specifies the information that must be included in this report, as well as the format the firm should follow when assigning the correction/removal reporting number. This number consists of the registration number for the responsible firm, the date of the report using MM/DD/YY format, a 3 digit sequential number for each report made on that date (i.e., 001, 002, 003, etc.), and the report type designation (i.e., "C" for a report of correction or "R" for a report of removal). 21 CFR 806.10.

You are reminded that a report of correction or removal should be reported to the appropriate FDA district office within 10 working days of initiating such correction or removal, and should contain the information required under 21 CFR 806.10.

13. If I file an adverse event report on the MedWatch 3500A form for an adverse event related to an LDT that I manufactured, do I have to file a corrections and removals report too?

The MedWatch 3500A form does not include all of the data elements required by 21 CFR Part 806 and therefore cannot replace the corrections and removals report. However, you may attach your 21 CFR Part 806 report to the MedWatch 3500A form.

Otherwise, the 21 CFR Part 806 report should be sent to the appropriate FDA District Office, and the MedWatch 3500A form should be submitted to FDA Headquarters.

14. Can I submit my reports electronically?

Yes, you can file your initial and supplemental reports with FDA in an electronic format. Information on sending initial and supplemental reports electronically is available at http://www.fda.gov/ForIndustry/FDAeSubmitter/default.htm. Instructions for electronic reporting are available at the electronic Medical Device Reporting (eMDR) home page at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/eMDR%E2%80%93ElectronicMedicalDeviceReporting/default.htm.

15. What are the supplemental reports that I must submit as an LDT manufacturer?

As an LDT manufacturer, you are obligated to file a supplemental report, using the MedWatch 3500A form, with FDA within one month of receiving additional or updated information on an adverse event that was not available or known at the time you submitted the initial MedWatch 3500A form. 21 CFR 803.56. You should report the supplemental information by providing the same user facility report number and manufacturer report number that was entered on the original submission by completing blocks *G.7 (Type of report) and G.9 (Mfr. report number)* and check the appropriate code in section *H.2.* Only new, changed, or corrected information should be entered on the MedWatch 3500A form. Information that was previously submitted should not be repeated. A detailed description of supplemental reporting requirements is provided in 21 CFR 803.56.

16. Are there additional MDR requirements that apply to user facilities that manufacture LDTs?

Yes. You need to amend your current MDR procedures to comply with your MDR reporting obligations as both an LDT manufacturer and user facility. 21 CFR 803.17.

User facilities and manufacturers are required to establish and maintain MDR event files. 21 CFR 803.18. For adverse events involving LDTs manufactured by your

clinical laboratory, you need to incorporate the additional requirements for manufacturers under 21 CFR 803.18(e).

17. How may I request exemptions or alternative reporting options as an LDT manufacturer?

Under 21 CFR 803.19(b) and (c), you may, as an LDT manufacturer, request an exemption from any or all of the reporting requirements of 21 CFR Part 803. FDA may, at its discretion, grant an exemption or alternative form of reporting adverse events. When the Agency grants an exemption or alternative form of reporting, it may impose other reporting requirements to ensure the protection of public health.

For information, contact the MDR Policy Branch at MDRPolicy@fda.hhs.gov

18. Where can I get additional information on user facility or manufacturer MDR reporting requirements?

Resources:

Find reporting information at:

- MedWatch: The FDA Safety Information and Adverse Event Reporting Program (http://www.fda.gov/Safety/MedWatch/default.htm)
- How to Report a Problem (Medical Devices) (http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm)
- MedWatch Coding Tools/Resource Files (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ReportingAdverseEvents/EventProblemCodes/default.htm)
- Medical Device Reporting (MDR) modules on the Center for Devices and Radiological Health (CDRH) Learn page available at: (http://www.fda.gov/training/cdrhlearn/default.htm).

You may also submit questions on MDR reporting to the MDR Policy Branch (MPB) at: MDRPolicy@fda.hhs.gov; or you may refer to the web site http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

APPENDIX A: FDA Notification Data Elements

To appropriately notify the FDA of all LDTs manufactured at an establishment, the owner/operator should provide information on the following data elements for *each* LDT manufactured at their establishment. Notification information should be submitted on-line through the FDA website.

1. **Laboratory Name**
   Indicate the legal name for your laboratory as you wish it to appear in FDA's records.

2. **Laboratory Contact Email Address**
   Indicate the contact email address for your laboratory as you wish it to appear in FDA's records.

3. **Test Name**
   Indicate the name of the test you are describing. Please note that the name can include a trade name or a general descriptor used by the laboratory to refer to the test.

4. **Monthly Test Volume**
   Indicate the number of clinical tests the laboratory conducts using this IVD per month.

5. **Intended Use**
   Provide a brief statement describing how your test is intended to be used. Please include a general description of the disease or condition that the test will provide information for diagnosis, treatment, prevention, cure or mitigation. Please note that a single test can have multiple intended uses.

   Example 1: The X urine test is an **immunoassay** designed for the **qualitative determination** of human chorionic gonadotropin (hCG) in **urine for the early detection of pregnancy**.

   Example 2: Test Y is a qualitative in vitro diagnostic test service, performed in a single laboratory, using the **gene expression profile** of fresh frozen breast cancer tissue samples to assess a patient's risk for distant metastasis. The test is performed for **breast cancer patients** who are less than 61 years old, with Stage I or Stage II disease, with tumor size <=5.0cm and who are lymph node negative. The result of Test Y is indicated for use **by physicians** as a **prognostic marker only, along with other clinicopathological factors**.

6. **Clinical Use of Test**
   Indicate which of the following categories demonstrate how the information generated by your test is intended to be used clinically. Please indicate all of the terms below that apply to how the information generated by your LDT is

intended to be used. If the "other" category is chosen, please specify the type of clinical use intended for the test.

Options:

- *Diagnosis*
- *Prognosis*
- *Monitoring*
- *Assessment of Risk*
- *Screening*
- *Organism Identification*
- *Therapy Selection/Monitoring*
- *Other*

7. **What is measured or detected (i.e. analyte, measurand, etc.)**
   Indicate any analytes that are measured or organisms that are detected by the test.

8. **Disease/Condition for which the diagnostic device is indicated**
   Indicate the type of disease or condition for which the test is used (i.e. cardiovascular disease, diabetes, breast cancer, etc.)

9. **Patient Population**
   Provide a brief description of the patient population in which the test is intended to be used.

   Example: Patients at high risk for developing type II diabetes.

10. **Does the patient population include pediatric patients? (<21 years old)**
    Indicate whether the LDT is intended to be used on patients under 21 years old.

11. **Sample Type**
    Indicate all of the sample types used for the test. Please note that a single test can utilize multiple sample types. If choosing "other" please specify the sample type used for the test.

    Options:

    - Serum
    - Plasma
    - Urine
    - Whole Blood
    - Cerebral Spinal Fluid (CSF)
    - Bone Marrow
    - Tissue
    - Organism Growth
    - Other

12. **Test Method**
    Indicate all test methods used for the test. Please note that a single test can utilize multiple test methods. If choosing the "other" category, please specify the additional test methods used for this IVD.

    Options:
    - Serology
    - Flow Cytometry
    - Fluorescence In Situ Hybridization (FISH)
    - Genotyping/Nucleic Acid Detection (human)
    - Immunohistochemistry (IHC)
    - Immunoassay
    - Mass Spectrometry
    - Microarray (i.e. genotyping, proteomics, Array-CGH or array comparative genome hybridization, etc.)
    - Nuclear Acid Amplification Test (NAAT) for microbial testing
    - High Performance Liquid Chromatography (HPLC)
    - Polymerase Chain Reaction (PCR)
    - DNA Sequencing
    - Other

13. **Is the test a modification of an FDA cleared/approved test?**
    Please indicate whether the IVD represents an FDA cleared or approved in vitro diagnostic test that has been modified in some way so as to affect device performance or intended use.

14. **If the test is a modification of an FDA cleared/approved test, what modifications were made?**
    If the IVD represents an FDA cleared or approved in vitro diagnostic test that has been modified in some way so as to affect device performance or intended use, please indicate what types of modifications were made to the FDA cleared/approved test. Please indicate all options that apply. If choosing "other", please provide a brief description of the modification.

    Options:
    - Intended Use Change
    - Instrument Change
    - Procedure Change
    - Software Modification
    - Sample/Specimen Type Change
    - Change in results interpretation reporting
    - Critical Assay Component Change
    - Other

APPENDIX B: ADVERSE EVENT REPORTING REQUIREMENTS

	What types of device-related adverse events must be reported?	Who should receive a copy of the report?	What is the time frame for reporting the adverse event?	Which sections of the MedWatch 3500A form must be completed?
1. An LDT that your clinical laboratory manufactured, that is, you are reporting as a device manufacturer of the LDT	• Deaths (21 CFR 803.50)	• FDA	• Within 30 calendar days after the day you become aware of the event.	For all reports: • A. Patient information; • B. Adverse event or product problem; (Skip section C) • D. Suspect medical device; • E. Initial reporter; • G. All manufacturers; and • H. Device manufacturers only.
	• Serious Injuries (21 CFR 803.50)	• FDA	• Within 30 calendar days after the day you become aware of the event.	
	• Malfunctions (21 CFR 803.50)	• FDA	• Within 30 calendar days after the day you become aware of the event.	
	• Remedial actions that were taken to prevent an unreasonable risk of substantial harm to the public *or* as requested by FDA. (21 CFR 803.53)	• FDA	• Within 5 work days after the day you become aware of the need for remedial action from any information, including any trend analysis, or have received a notification from FDA requesting 5-day reports	
2. A device that is not an LDT manufactured by your clinical laboratory, that is, you are only reporting as a user facility. If you are reporting as user facility and manufacturer, you must fulfill the reporting requirements	• Deaths (21 CFR 803.30)	• FDA *And* • Device Manufacturer	• Within 10 work days after the day you become aware of the event.	For all reports: • A. Patient information; • B. Adverse event or product problem; (Skip section C) • D. Suspect medical device; • E. Initial reporter; and • F. For use by user facility/distributor-devices only.
	• Serious Injuries (21 CFR 803.30)	• Device Manufacturer *Or* • FDA when the device manufacturer is unknown	• Within 10 work days after the day you become aware of the event.	
	• May voluntarily report	• FDA	• Not required. Voluntary reports may be submitted at any time. • Link to 3500 voluntary report	

of this section <u>and</u> those listed in section 1 above in this chart.	malfunctions	*Or* • Device Manufacturer	form https://www.accessdata.fda.gov/scripts/medwatch/