AdvaMedDx
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January 30, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2011-D-0360; Draft Guidance for Industry, FDA Staff, and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests

Dear Sir or Madam:

On behalf of AdvaMedDx, a Division of the Advanced Medical Technology Association (AdvaMed), we provide these comments on the Food and Drug Administration (FDA) "Draft Guidance for Industry, FDA Staff, and Clinical Laboratories on Framework for Regulatory Oversight of Laboratory Developed Tests" (hereinafter "guidance"). Our comments related to the FDA "Draft Guidance for Industry, FDA Staff, and Clinical Laboratories on FDA Notification and Medical Device Reporting for Laboratory Developed Tests" are also contained herein under sections IV.E and IV.F.

AdvaMedDx member companies produce advanced, *in vitro* diagnostic tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMedDx is the only multi-faceted, policy organization that deals exclusively with issues facing *in vitro* diagnostic companies in the United States and abroad. Our membership includes manufacturers engaged in the development of innovative diagnostic tests supporting the advancement of the public health and personalized medicine from infectious disease to cancer care to safe and efficacious drug therapy (i.e., companion diagnostics) in a variety of settings, including laboratories, hospitals, and doctor's offices.

GENERAL COMMENTS

AdvaMedDx commends the FDA (or "Agency") for the development of this guidance, which helps address critical public health gaps in oversight of laboratory developed tests (or "LDTs"), supports transparency to the public on scope and use of LDTs, and implements a risk based transitioned approach that minimizes disruption and promotes innovation in safe and effective *in vitro* diagnostics.

The diagnostics industry is a cornerstone of the modern health care system, providing vital information at every stage from screening to diagnosis to selection of treatment. Rapid advances are being made that are paving the way for more personalized, targeted patient care.

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At the same time, there have been rapid changes proliferating in the complexity, risk, and marketing of LDTs and the regulatory status quo has been universally recognized as insufficient. The current two-tier regulatory system that differentiates between LDTs and traditional manufacturer-developed tests solely on the basis of the type of developer, without regard to patient risk, is fundamentally unsustainable and must be modernized to support the public health and robust development of new, safe and effective diagnostics. Maintaining two very different oversight mechanisms for tests that raise identical risks to patients, is bad public policy, provides an opportunity to use tests in clinical settings with little to no clinical validity, and stifles investment in high quality products that can stand up to FDA review. It is imperative that the FDA (or "Agency") adopt a risk based regulatory approach for all diagnostics, regardless of where a test is developed.

To date, FDA has exercised enforcement discretion for LDTs, meaning that FDA has not enforced applicable regulations with respect to these tests and has not been reviewing LDTs to assure safety and effectiveness. LDTs also have not been subject to numerous other aspects of FDA regulation that are designed to protect patients. When FDA began regulating medical devices, LDTs generally were relatively simple, low-risk tests and FDA exercised enforcement discretion. Now, LDTs encompass even the most advanced molecular diagnostics, such as higher risk tests that are essential for safe and effective use of cancer therapeutics or a critical determinant in the treatment of serious, life-threatening diseases. In order to ensure access to safe and effective LDTs, the FDA has announced its plans to exercise its existing enforcement discretion authority over LDTs through implementation of a risk based regulatory framework.

Laboratories are regulated by CMS under CLIA – the Clinical Laboratory Improvement Amendments of 1988. CMS itself has acknowledged the clear differences between CLIA oversight of laboratories and FDA oversight of diagnostic tests, noting FDA's unique role, scope, and qualification to assure the safety and effectiveness of tests. CLIA regulations focus on laboratory practices, including testing procedures, certification, and personnel. As CMS has explicitly stated, CLIA does not regulate the safety and effectiveness of tests. CLIA is not a substitute for FDA oversight. Critical features of FDA oversight are not covered under the CLIA program, which regulates good laboratory practices and is required for all laboratories performing tests, including FDA-approved/cleared tests and LDTs. Furthermore, CMS does not have the expertise or resources to oversee LDTs in the same manner as FDA. Unlike FDA oversight of diagnostics, CLIA:

- Does not regulate the safety and effectiveness of diagnostic tests;
- Does not require premarket review of tests;
- Does not require demonstration of clinical validity (whether the test is meaningful for clinical decision making);
- Does not require systematic adverse event reporting;
- Does not have a process for recalls (corrections or removals).

Under FDA's proposed framework to address gaps and ensure transparency on the scope and use of LDTs, LDT developers will need to provide information to the public on available LDTs and associated facilities. This is an important and critical step. Up to this point, this information has only been available for diagnostic tests that have listed their facilities or received clearance or approval from FDA.

We commend FDA's efforts to take this critical step to support patient care and robust product development while ensuring that well-recognized gaps in oversight are addressed. Furthermore, we thank FDA for its hosting of public meetings, provision of multiple opportunities for stakeholder input, and development of a thoughtfully crafted, risk based phased proposal that incorporates numerous comments from diagnostic developers and supports access to unmet and special needs tests. Patient-centered, risk based regulation that facilitates innovation for safe and effective diagnostics is of paramount importance. Patients deserve no less.

A test is a test and presents the same risk for patients regardless of whether it is developed by a traditional manufacturer or a laboratory. Potential harms to patients whose tests return incorrect results include unnecessary treatments with their accompanying costs and side effects and treatment delay or failure to obtain appropriate treatment, all of which lead to worse outcomes for those patients.

We note that the guidance, as drafted, appears to limit the assistance that traditional manufacturers are able to provide to assist LDT developers as the framework is implemented and submissions are brought to FDA. If FDA made clear that such activities were not viewed as inappropriate promotion but were instead a "safe harbor," interested manufacturers would likely be willing to serve as helpful resources to LDT developers in terms of lending experience or assistance for those developing LDTs and ultimately going through the FDA premarket process. We believe this clarity and associated revisions in the guidance would encourage collaborative and constructive engagement of the diagnostic community to support safety and effectiveness of these medical products and optimal adoption of the guidance.

Imposition of a regulatory system for tests (i.e., LDTs) can be expected to cause some disruption, but we believe FDA can balance both patient safety and continued and future innovation through appropriate risk based oversight. Patient-centered, risk based regulation that facilitates innovation for safe and effective diagnostics tests is of paramount importance. Patients deserve no less. FDA has addressed this with the thoughtful development of a proposed risk based LDT oversight framework that reflects a number of features to ease transition for the laboratory community and support test continuity. Such risk based approach includes an appropriate phase-in time frame that allows for smooth implementation while supporting clarity in the marketplace, focus on higher risk tests, and continued use of enforcement discretion for many LDTs, particularly in academic medical centers, to minimize disruption and support test continuity. Also, tests undergoing premarket review may notably remain on the market during the review process, which will aid transition of

tests under FDA oversight. For lower risk tests for which continued enforcement discretion is proposed, focus is on transparency and appropriate premarket and postmarket controls rather than premarket submissions.

Indeed, we appreciate the flexibility that FDA has provided in the guidance, and the recognition that a risk based approach is the appropriate implementation route. At the same time, we believe that additional measures can and should be implemented for diagnostics at large to further support robust innovation now and into the future. AdvaMedDx has long advocated for a flexible, risk based approach to the regulation of all diagnostic tests—whether developed by manufacturers or clinical laboratories—based on the risk associated with the use of the test. This would best leverage FDA resources, well align submission requirements, and help pave the way for an overall improved risk based regulatory process for all diagnostics. All available FDA pathways to promote development of new cleared and approved diagnostic technologies should be implemented to aid the regulatory process and support good faith efforts by all diagnostic innovators.

As part of FDA's request for feedback, AdvaMedDx has provided recommendations on specific provisions and best implementation of a modernized risk based regulatory approach for diagnostics. We note that there are several areas within the draft guidance where the new regulatory policies should be clearly delineated for all diagnostics tests as part of an overall risk based approach for diagnostics, including flexible, risk based evidence expectations (e.g., use of scientific literature to support clinical validity), better leveraging of third party review program for moderate-risk devices, appropriate exemption of low-risk, well-established tests from premarket review, improving regulatory process for rare disease diagnostics, and exploring additional accelerated pathways to promote future innovation in unmet and special needs as part of an overall modernized approach. Comments are also provided to improve clarity and support smooth implementation.

SPECIFIC COMMENTS

AdvaMedDx's specific comments on the draft guidance follow, which provide more detailed recommendations and several points for additional clarification in issuing final guidance. A line-numbered version of the draft guidance is also attached for your reference.

I. Definition of "Laboratory Developed Test" and Scope of Guidance

As previously discussed, a test is a test and presents the same risk for patients regardless of whether it is developed by a manufacturer or a laboratory. Potential harms to patients whose tests return incorrect results include unnecessary treatments with their accompanying costs and side effects and treatment delay or failure to obtain appropriate treatment, all of which lead to worse outcomes for those patients.

FDA has clear regulatory authority over LDTs as it does with all diagnostic tests (otherwise referred to as "*in vitro* diagnostics" or "IVDs"). Like other IVDs, LDTs are a subset of

devices under the Food Drug and Cosmetic Act ("FDCA") and are subject to regulatory oversight by FDA. FDA has the authority to regulate all diagnostics, whether made by manufacturers or clinical laboratories. Tests present the same risk/benefit profile for patients no matter where a test is made.

Diagnostics tests are produced by manufacturers for distribution to laboratories and other users, produced by laboratories for distribution to additional laboratories, or produced and used in a single laboratory for use only within that laboratory (the latter two are treated as LDTs for purposes of FDA's proposed framework). Notably, FDA provided flexible, risk based application and phased-in transition time under the draft guidance even for tests which do not meet the definition of LDTs (i.e., produced by laboratories for distribution to additional laboratories).

A. Assistance to Laboratories From Other Developers

The guidance indicates that an IVD intended for clinical use that is designed, manufactured, and used within a single laboratory will remain an LDT subject to enforcement discretion as outlined, even if the LDT contains an analyte-specific reagent (ASR) and general purpose reagents manufactured by third parties. The guidance proposes, however, to negate a test from being an LDT if the LDT is designed or manufactured in part outside of the laboratory that offers and uses them. In particular, this applies to a laboratory that contracts with a manufacturer to produce a "key component" used in its test. This definition is confusing as many LDTs and/or part of the LDTs (e.g., reagents and platforms) are manufactured by contract manufacturers or other IVD developers. Maintaining this approach is in the best interests of the public health in that other developers who are knowledgeable about the assays/panels and have significant expertise in manufacturing them and their components can support laboratories' appropriate development and use of tests. This is parallel to other diagnostic devices, which are increasingly comprised of a system of components, including reagents, hardware, and software. In this regard, we believe that use of such components in LDTs should be permitted, particularly if that component provided by another developer (or via supplier) is subject to FDA Quality System Regulation (QSR).

As FDA recognizes in page 5 of its guidance, some laboratories currently obtain assistance from third parties. Such assistance should not be prohibited, but rather, should be encouraged because it serves to foster FDA's goals of ensuring that diagnostics used in the provision of health care, whether developed by a laboratory or a traditional IVD manufacturer, comply with appropriate regulatory controls to assure that they are safe and effective. Importantly and from a patient safety perspective, we urge FDA to recognize and include within the scope of LDTs test systems those designed and/or manufactured utilizing the assistance of other developers. In particular, this will aid laboratories that may need to build infrastructure to meet FDA standards. Moreover, we believe that it will encourage a greater level of test innovation by combining the expertise of laboratories and other developers, whether traditional or other manufacturers. As other developers are allowed to

outsource and engage in contract manufacturing, the language in the current guidance appears to be overly restrictive.
Therefore, the guidance should be revised to remove the example in lines 153-154 and instead state that in considering design of an LDT, "if a test, once validated, would be used by a single laboratory to provide clinical diagnostic results, it would constitute an LDT regardless of whether a component is manufactured by a third party."

In addition, we propose FDA consider removing the words "designed and manufactured" from the definition of LDT in line 127 and throughout the document. In any case, FDA must broaden the understanding of the term "single laboratory" such that "single laboratories" can obtain assistance from other developers in the design and manufacture of LDTs. Consistent with this, FDA might also consider explaining accountability/responsibility associated with specification development (i.e., contracting to produce a key component according to its specifications to be used in its device) to improve clarity in the proposal.

AdvaMedDx would also recommend expanding the question and answer section of the document to address questions pertaining to interactions between laboratories and traditional manufacturers. For example, we recommend including the following: "When would an IVD manufacturer function as a supplier or a component contract manufacturer for a clinical laboratory? An IVD manufacturer may function as a supplier or a component contract manufacturer for a clinical laboratory that produces diagnostics (e.g., reagents and various classified instruments)."

Further, FDA should take care not to infer that legally marketed Research Use Only (or "RUO") products, which are not intended for diagnostic use, should not be sold to laboratories or take unfair or punitive action on manufacturers of legally marketed RUO products, e.g., place manufacturers in an untenable position of policing customers' use or what might be incorporated into LDTs. While FDA implemented RUO final guidance generally consistent with industry expectations, we reiterate that RUO products play an important role as promising results from early research can later lead to the development of an investigational product (IUO) and, finally an IVD. FDA should take care not to discourage legitimate scientific research and exchange between manufacturers and their laboratory customers. Such action could potentially harm the public health by slowing product innovation that flows from such products, potentially disrupting important research, and discouraging the flow of information about any potential issues with products. Also, this exchange and technical support should be encouraged to facilitate laboratories in the transition to FDA oversight and good faith efforts to gain test approval and clearance. FDA implementation of quality systems for many LDTs should also mitigate concerns as LDTs will be manufactured under the same or harmonized quality system used for cleared and approved devices.

B. Use in Clinical Trials

While FDA indicated in an October 23 webinar that its policy has not changed and LDTs

used in a clinical trial of a therapeutic product for screening/eligibility are subject to the guidance, we recommend clarification in the guidance as they are "intended for clinical use." We also note there appears to be an incorrect perception that companion diagnostics requirements and FDA oversight do not apply to LDTs used in early exploratory trials even where selection is occurring, which is concerning from a patient safety and risk perspective.

To provide clarity, additional language might be added as follows: "The guidance applies to those LDTs (as defined in the Guidance) that are intended for clinical use." LDTs should follow the IDE regulation per 21 CFR 812.

II. Gaps in Regulatory Oversight/Additional Considerations

A. Clinical Validity

We appreciate FDA's outlining of elements for FDA review for diagnostic tests. We concur that FDA oversight of safety and effectiveness includes review of analytical and clinical validity and agree with these standards. FDA must ensure the same standards of analytical and clinical validity are met for all diagnostics tests. At the same time, we believe it is important to clarify in this guidance that clinical utility is not a requirement for FDA approval or clearance.

In recent years, FDA has held IVD manufacturers to a higher standard in some cases, requiring valid scientific evidence of clinical utility, leading to substantially large and expensive clinical trials. To ensure uniformity of evidence requirements, we urge FDA to clarify in all cases that the standard is clinical validity, regardless of the intended use of the test, or where it is developed or manufactured.

Notably and as discussed in further detail in our comments, we greatly appreciate FDA's recognition in the guidance that clinical validity often can be established through peer-reviewed, scientific clinical literature. We encourage FDA to apply this principle where at all possible for all diagnostic tests, whether LDTs or other IVDs, to best leverage the science, reduce clinical data requirements, and support new diagnostic product development in the U.S. under a modernized risk based regulatory framework.

B. Test Report Transparency

FDA's comment on lines 354-361 that "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" is an important one.

Where LDTs will continue to be extended enforcement discretion, FDA should consider requiring a statement that accompanies the test result that indicates the test has not been cleared or approved by FDA. This would be similar to that which is currently required for

ASRs. This information would support open and transparent communications with the medical community and support the public health. We encourage FDA to consider whether such information should also be available to the patient or the physician prior to ordering a test and not just after the test is conducted, but LDT registration and listing should mitigate this concern once in place.

C. Quality System Requirements

We agree as referenced in lines 373-375 that "appropriate quality controls through compliance with the FDA Quality System Regulation (QSR) under 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." We also concur, as referenced in lines 1142-1144, that laboratories should be encouraged to "begin working towards building elements of the QS regulatory requirements into their practices as these requirements apply to the design and manufacture of LDTs."

At the same time, it is not clear to what extent laboratories will be required to follow Part 820 requirements and what is meant by the term "appropriate". We encourage FDA to provide more detail regarding the requirements that will apply to laboratories, either in this draft guidance, or in a separate document specific to quality system requirements. The most fundamental difference between CLIA and FDA QSR is design control in the design and manufacturing of diagnostic tests. In that vein, we suggest that lines 527-528 be revised to state "… when a PMA is submitted or FDA issues a 510(k) clearance order, with the exception of design controls which occurs during product development, for the LDT." Furthermore, we suggest FDA revise lines 1144-1145 to read more clearly as follows: "S~~pecifically, the Agency encourages laboratories developing~~ New LDTs, developed after FDA issues the final guidance for which FDA has called for a PMA or 510(k), would be expected to conform to ~~implement~~ design controls (21 CFR 820/30(a)-(j)) during product development. ~~and remaining elements should be in place by no later than the time of submission) and [w]hen applied appropriately, the design control elements described by the QS reg ensure a more robust device design with fewer device defects and recalls.~~"

We would also welcome further discussion on how to best implement quality system requirements for clinical laboratories and by whom and how quality system inspections might be conducted for clinical laboratories developing LDTs. FDA and CMS via CLIA have different roles and regulatory goals. FDA regulation addresses the safety and effectiveness of the diagnostic tests themselves and the quality of the design and manufacture of tests. CLIA regulates the quality of the clinical laboratory. We note there may be opportunities, however, to implement a quality system for LDTs that leverages CMS current oversight of laboratories.

We understand that FDA plans to implement QSR in an incremental, phased approach and there will be further discussion on how best to move forward. While we acknowledge that it

will take time and expertise for laboratories to implement QSR and FDA should make all efforts to assist LDT developers in this endeavor, implementation of a quality system for LDTs to support safety and effectiveness through the continuous product lifecycle from test development through the postmarket phase is essential and not currently in place for LDTs under CLIA.

III. Risk Based Approach Toward Oversight of LDTs

A. Risk Based Classification

AdvaMedDx has long called for FDA to modernize its regulation by ensuring risk based regulation of all diagnostics, regardless of where they are made. Risk posed to a patient is irrespective of where a test is developed. As it does for all medical devices, FDA regulates diagnostic tests according to risk. The classification process is well described in the FDCA and its codified regulation. For diagnostics, risk assessment considers harm that could occur if test results are incorrect. We note the majority of diagnostics are low- and/or moderate-risk devices based on the nature of the claims made for them (i.e., intended use), and therefore, respectively Class I and II devices. Therefore, the majority of diagnostics does not require premarket approval (PMA) and are subject to the premarket notification (or 510(k)) process. We also note that newer regulatory tools such as the *de novo* 510(k) process have allowed for improved, appropriate risk based review of tests in addition to the traditional 510(k) process. Through unified treatment and triage of all diagnostic tests through the classification and regulatory process, FDA can and will achieve a truly modernized approach for diagnostics that supports the public health and fosters new safe and effective diagnostic innovations for patients.

Consistent with risk based classification, we note that higher risk tests generally comprise tests where a false result could lead to incorrect and harmful clinical management, an unnecessary invasive procedure, or failure to follow up a serious condition. Examples include tests for cancer diagnosis, tests that directly or very strongly influence management of serious disease, tests for serious or fatal communicable diseases and most companion diagnostics. The underlying factor for determining higher risk tests is the nature of the claims made for them (i.e., intended use). These tests are distinguished from tests where there are multiple findings used to direct clinical management and where each finding has a specific weight in disease management. They are also distinguished from most tests used to monitor already detected and diagnosed disease and genetic tests where the phenotype is already known and is now being confirmed genetically. These tests are also distinct from low-risk, well-established tests such as cholesterol, iron, and nicotine as well as urine and blood collection kits.

In line with AdvaMedDx's approach, FDA proposes a risk based, phased-in approach for implementation of oversight that appropriately focuses the Agency's resources on tests that pose the highest risk to patients. Further, FDA plans to phase in this oversight over a minimum of nine years following finalization of the LDT guidance.

AdvaMedDx further suggests that FDA consider additional exemptions from premarket review for low-risk, well-established tests for all developers, whether LDT or traditional manufacturers. This will support FDA risk based review and focus on higher risk products while maintaining robust premarket and postmarket controls for low-risk, well-established tests. While a number of IVDs are currently exempt, further products are ripe for exemption and should be moved to the Class I and II exempt lists.

B. Overall Risk Based Regulatory Approach for Diagnostic Submissions

As part of an overall risk based approach, AdvaMedDx has long reiterated that tests should be cleared or approved through an approach where the data submission requirements are commensurate with the level of risk of the test. With respect to specific application of risk based submission requirements for all diagnostics, FDA can and should consider:

1) Clinical use of a test (risk associated with how the test is used in the treatment of patients)—e.g., seriousness or prevalence of the condition, prevalence of condition, reversibility of intervention, or standalone use (not supplementary to other clinical information);
2) Novelty of analyte (the substance that is undergoing analysis or is being measured);
3) Novelty of technology (or test platform);
4) Experience or training of the person performing the test; and
5) Factors that reduce or mitigate risk—e.g., scientific information, literature, general and/or special controls.

The first four considerations are risk elements. Data that mitigates risk should be considered as available for all four categories and may be different (e.g., literature for 1 and 2, experience of FDA for 3, human factors studies/design elements for 4). Further details are contained in our comprehensive AdvaMedDx risk based approach proposal for diagnostics regulation.

The last consideration is of particular note as FDA specifically recognized in its draft guidance that literature may be considered to support clinical validity. We are pleased with such recognition and further discussion follows on this point in IV.A.

IV. LDT Framework

A. Use of Clinical Literature

We agree with FDA that clinical validity often can be established through clinical literature alone, or through clinical literature with limited study data. We appreciate FDA's explicit recognition of clinical literature as an acceptable source of valid scientific information to promote investment and innovation for diagnostics as part of an overall efficient, risk based approach to regulation. Such literature should be fairly considered and not require further

independent review of the underlying data. Further, this policy should apply equally to laboratories and traditional IVD manufacturers as a means of reducing the need for clinical trials and establishing clinical validity regardless of who submits a diagnostic test. The risk is the same and therefore tests should be treated the same for regulatory purposes.

Therefore, the guidance should be revised as follows on line 466: "When an LDT's or other IVD's analytes/markers that are measured/accessed have had their clinical validity already established in the literature, FDA believes that 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 or other IVD. FDA intends to work with the laboratory community, traditional manufacturers, the health care professional community, and other stakeholders to identify those ~~LDTs~~ IVDs for which the clinical validity of the analyte/marker has already been established in the literature."

Similar revisions are needed on lines 566-568 to state "…reduce the need for additional clinical studies to show clinical validity for LDTs and other IVDs where the analytes/markers that are measured/assessed have had their clinical validity established in the literature."

B. Advisory Panels

We support FDA's use of advisory panels, which are part of FDA's established classification process (referenced in lines 634-641). Furthermore, we agree with the need to identify LDTs that are in the market and to collect the necessary data to enable robust and productive expert advisory panels to develop recommendations as referenced in the guidance Section D.3.

As FDA moves forward with advisory panels, we would encourage FDA to include both laboratories and traditional IVD manufacturers within those expert panel discussions, as presumably any new classification will apply equally to all IVDs, regardless of who develops them. We also encourage the selection of panels to be transparent and these meetings to be open to the public.

C. Clear Treatment of Intended Use

AdvaMedDx commends FDA for its commitment to the public health through a risk based regulatory framework that appropriately focuses on specific intended use to help guide classification and regulatory treatment, irrespective of where a test is developed. To further enhance clarity in the document, we recommend that FDA expound on what is included within the category of high-risk LDTs referenced in lines 453-454. Importantly, the guidance needs to provide a better description or examples of a laboratory developed test having the "same intended use as a cleared or approved product" and "same intended use as a cleared or approved companion diagnostic." For example, will an intended use to detect a particular biomarker for which an approved companion diagnostic test is available be

included if the laboratory does not specifically claim that the test is a companion? Also, FDA should also consider different indications. Any approach should be consistent. Where FDA would consider an additional indication a new intended use for other diagnostics, the Agency should do so for LDTs.

We are concerned that the definition of "same intended use" may be subject to a wide range of interpretations given the differences that may exist in the intended use statements. This could result in confusion about which tests need to be submitted as part of the highest risk category of devices. Several possible situations exist:

- A laboratory could develop a test that detects the same analyte as a cleared/approved product, but with a different indication for use. For example, the cleared/approved test could be used to monitor viral load levels to assess the effectiveness of a given therapy after the onset of disease, whereas the LDT could be used to determine when to initiate treatment based on the viral load level. Another example is evident in the evolution of Human Papilloma Virus (HPV) testing. While the test reagents and assay methodology have remained the same, the indications for use have changed from Aytypia Squamous Cells of Underdetermined Significance (ASCUS) triage to adjunctive to primary screening.

- A laboratory could develop a test that detects the same analyte as a cleared/approved product with the same indication for use but utilizes a different sample type. For example, the cleared/approved test could be used with whole blood, whereas the LDT could be used with plasma.

- A laboratory could develop a test that detects the same analyte as a cleared/approved product, but also detects other analytes. For example, the cleared/approved test could be used to identify the presence of one mutation for a companion diagnostic indication, whereas the LDT could be used to identify the presence of multiple mutations, only one of which is used in the cleared/approved test.

Consideration should be given to strengthening the definition of "same intended use", perhaps though the inclusion of examples which would make the distinction between what is considered the same and what is different. Furthermore, it is unclear who is responsible for deciding if the intended uses are the same or different under the LDT framework, and the mechanism to seek resolution.

Similar questions related to intended use are presented in other sections of the guidance. For example, FDA references in lines 853-854 "whether there is no FDA cleared or approved IVD available for that specific intended use." Equivalent device is defined as having the same "specific intended use." Clarification is needed for whether the same technology or different technologies makes any difference in determining equivalency. IVD manufacturers must consider this issue when developing regulatory submission strategies that identify whether the device fits a premarket notification, *de novo* or premarket approval submission

pathway. For example, for a test to aid in the diagnosis of chronic lymphocytic leukemia there are molecular methods and flow technology. If one gets approved/cleared, does the other have to comply with premarket requirements? It would also be helpful to clarify, consistent with FDA discussion on its October 23 public webinar, that if a panel contains a marker that is approved as a companion diagnostic, FDA would consider at least that marker to be a companion diagnostic.

Of key importance, the guidance should also provide clarity to laboratories, whether in its own section or perhaps the notification/registration and listing section, that LDTs cannot be promoted for a purpose other than their listed intended use and changes to that intended use with no FDA clearance or approval cannot be promoted and ultimately may impact risk classification and pathway to clearance or approval. In addition, it may trigger enforcement by FDA. This may not be intuitive to laboratories, which may assume that other uses would not necessarily entail regulatory oversight or compliance responsibilities. Explicit language might be added, such as "[d]evelopers should be aware that if FDA finds evidence of new intended uses based on promotional practices, the product may fall into another category." It may also be useful for FDA to cite 21 CFR 801.4 or reference in a footnote.

D. Third Party Review

We strongly support FDA's proposal to leverage the third party review program for moderate-risk devices. Such a program is within FDA's existing regulatory programs and can be a valuable tool for both FDA and industry. We encourage FDA to make the policy equally available for all diagnostics tests, regardless of developer (LDT or traditional IVD manufacturer). However, FDA should take care to ensure that reviewers are not required to conduct a secondary review of the third party review reports, as has sometimes been the case. We appreciate FDA's important third party review program, which we anticipate will give both traditional IVD manufacturers and laboratories the option of using those third parties to review their diagnostic tests as part of an overall modernized approach.

E. *Notification/Registration and Listing*

We strongly support address of this key postmarket oversight gap for LDTs, which is also covered in FDA's draft guidance "Notification and Medical Device Reporting for Laboratory Developed Tests" (or "Notification/MDR guidance") issued October 3, 2014. Under FDA's proposed framework to address gaps and ensure transparency on the scope and use of LDTs, LDT developers will need to provide information to the public on available LDTs and associated facilities via opting to use notification and/or registration and listing. This is an important and critical step. Up to this point, this information has only been available for diagnostic tests that have listed their facilities or received clearance or approval from FDA.

In addition to providing transparency to the public on the scope and use of LDTs, this information will be necessary for FDA to collect the necessary data to enable robust and productive expert advisory panels to develop recommendations for classification. While

notification is provided as a tool, we note that registration and listing accomplishes the same intent and should be sufficient. We support this important activity by FDA to collect this critical information, but we note a parallel system for LDTs is not necessary for purposes of regulatory oversight. Alternatively if FDA moves with providing this flexibility and additional avenue for this information at an early juncture, this program should simply be noted as an "alternative" program rather than "voluntary" program as choosing not to notify FDA will mean a laboratory will still need to register and list as part of FDA's existing and appropriate oversight authority. As part of any notification, FDA may wish to request cross-reference to a laboratory's CLIA certification to ensure that laboratories developing such tests have appropriate certification for minimally performing such tests.

FDA requested specific feedback on the question of whether a single notification from a clinical laboratory network for a test is sufficient for purposes of reporting. While this pertains to a scenario that falls outside of the FDA definition of LDT, we support such efficiency provided that the laboratory indicates in the notification to FDA that the test is offered at multiple sites and indicates which sites for accuracy and transparency to healthcare providers, patients, and the greater public.

Furthermore, it is important that FDA define "significant changes" in lines 628-629. For the purpose of notification and/or registration and listing of diagnostic tests, it is important that FDA apply a uniform definition to when a change to a test must be reported to FDA regardless of developer in accordance with regulation.

F. *LDT Medical Device Reporting*

Beyond critical oversight of the safety and effectiveness of tests, FDA's proposed framework would require that all LDT developers comply with medical device adverse event reporting requirements. We unequivocally support address of this key postmarket oversight gap for LDTs in FDA's Notification/MDR guidance. This guidance outlines long-established, existing requirements for adverse event reporting. Adverse event reporting enables necessary corrective action and helps to prevent injury and death by alerting the public when potentially hazardous devices are discovered. Analyzing adverse event reporting also enables detection of unanticipated events and user errors, monitoring and classifying of recalls, updating labeling information, and developing educational outreach. Using adverse event report data, FDA can detect problems previously unknown as well as problems with similar devices or device categories.

We simply recommend that FDA use more precise language as written in 803.3 to avoid confusion or potentially different interpretations of meaning. Specifically, line 717 should be revised to state "…information ~~to~~ that reasonably suggest a reportable adverse event has occurred (21 CFR 803.3)." Further, line 724 should be revised to "has malfunctioned and this device or similar device that you market ~~the malfunction~~ would be likely to cause or contribute to a ~~reportable~~ death or serious injury, if the malfunction were to ~~should it~~ recur (21 CFR 803.50)" to better reflect language in 21 CFR 803.50 (a)(2). We also suggest that

line 724 add a footnote for the term "malfunction" to the definition from 803.3. All other key terms appear to be defined and this would help promote understanding. FDA's Footnote 23 on line 498 should also specifically reference adverse event reporting under 21 CFR Part 803 for clear and uniform regulatory terminology.

AdvaMedDx also recommends creation of a new section in this guidance or the Notification/ MDR guidance that clarifies specifically how IVD manufacturers should address adverse event reporting in cases where LDT developers make modifications to FDA-cleared or approved devices. Medical device manufactures must report adverse events for their products according to the requirements in the Medical Device Reporting (MDR) regulation (21 CFR Part 803, Subpart E). The MDR regulation requires the manufacturer of a medical device to submit reports to the FDA whenever they become aware of information that reasonably suggests that a device they market may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction would be likely to cause or contribute to a reportable death or serious injury should it recur. Under the LDT Framework, clinical laboratories manufacturing LDTs would be required to follow the same regulation as traditional IVD manufacturers.

While the Notification/MDR guidance clearly indicates that LDT manufacturers must fulfill the reporting requirements when they use FDA-cleared/ approved devices modified by their laboratory, the obligations by the IVD manufacturer in such cases are unclear. The IVD manufacturer may or may not be aware that their FDA-cleared/approved device is being used as part of another IVD device. While any modifications beyond the claimed intended use of the FDA-cleared/approved device should be the responsibility of the LDT manufacturer, the IVD manufacturer is obligated to report adverse events irrespective of the intended use. This may lead to a duplication of reporting by both the LDT manufacturer and the IVD manufacturer for the same adverse event. In addition, it is not clear who would be responsible for any complaints or root-cause investigations for FDA-cleared/approved devices modified and manufactured by the clinical laboratory. This level of specificity in the guidance(s) would facilitate appropriate adverse event reporting when LDT developers make modifications to FDA-cleared or approved devices and clarify responsibility of LDT and other IVD developers. We will provide further comments on modifications with respect to approved or cleared IVDs later in our comments under Section V.D.

V. Premarket Review Requirements

As previously stated, we appreciate FDA's commitment to the thoughtful development of a proposed risk based, phased LDT oversight framework that reflects a number of features to ease transition for the laboratory community and support test continuity. Notably, FDA proposed continued use of enforcement discretion for a substantial scope of LDTs to minimize disruption and support test continuity. We strongly support efforts to ensure smooth transition and access to rare disease diagnostics and tests that address unmet needs and provide specific comments on these and additional categories contained in the guidance.

We believe a proper oversight system that balances both patient safety and continued and future innovation can be well accomplished under appropriate risk based oversight by FDA. FDA has made tremendous progress in improving the regulatory process for diagnostics and its recent proposed framework for LDTs is a critical step forward. However, we note the importance of exploring additional opportunities that may exist to improve the overall diagnostics landscape. As previously discussed, AdvaMedDx recommends that FDA conduct a review of IVD products to consider additional exemptions from premarket review for low-risk, well-established tests for all developers, whether LDTs or traditional manufacturers. As outlined in our earlier comments on risk based diagnostic submissions, all efforts should also be undertaken by FDA to support data submission requirements commensurate with the level of risk of the test. Reviewer training also continues to be critical with respect to FDA application of a least burdensome approach to ensure requiring only the evidence necessary to evaluate all IVD submissions as part of an overall, modernized risk approach for all diagnostics. FDA can and should leverage all available pathways—irrespective of developer— to support bringing new safe and effective products to the market, improve premarket and postmarket balance, and spur access to specialized diagnostic tests categories, particularly rare disease.

A. Diagnostics Used for Rare Diseases

The draft guidance draws attention to one significant policy problem in need of attention. FDA's application of the rare disease pathway, Humanitarian Use Device (HDE), has been a significant obstacle for the development of diagnostic devices for rare diseases and must be improved to serve as a meaningful pathway for diagnostic developers for rare disease. Under the FDCA, an HDE is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the U.S. per year. To obtain approval for an HDE, companies submit an HDE application to FDA, which has special requirements. As FDA would likely agree, this hard cap at 4,000 individuals tested is excessively restrictive. Provisions related to the statutory cap continue to be interpreted very narrowly by FDA and block the development of diagnostic devices for rare diseases and conditions. There is no scientific evidence behind the original statutory 4,000 person cap. In particular, it is a significant hurdle for the development of diagnostic devices for rare diseases to demonstrate the number of patients that would be subject to diagnosis by the device, rather than the number of individuals affected or manifesting the rare disease. If a diagnostic test were developed to diagnose patients with a condition that manifests in 4,000 people or less per year, it is quite likely that physicians would prescribe the test more than 4,000 times a year to diagnose those with the rare disease.

To address this limitation and rather than an exemption for all HDE LDTs that is irrespective of relative risks posed by individual tests, we recommend flexibility to FDA to allow all HDEs that benefit patient populations that exceed the 4,000 limit. Applicants would be required to demonstrate that the severity of the disease or condition is such that the public health requires a greater availability of the device to treat or diagnose that population. Such

optimal provision would clarify that in the case of IVDs, the 4,000 person limit does not apply to the number of tests needed to treat or diagnose a specific patient population.

In terms of alternatives, another option might be to raise the number to a more reasonable number that promotes the development of rare disease diagnostics. Further, one might establish criteria that support reasonable investment in rare disease diagnostics while making clear that the pathway is not intended for blockbuster products or screening the population at large. Many options are available for FDA's consideration, and stakeholders are in large agreement that the current limitation has not served patients well in research and development of diagnostics for rare diseases.

We appreciate FDA's willingness to consider comments on all aspects of the proposal and FDA's conundrum with respect to the current HDE provision and the applicability of the extremely low tests cap and its impact on diagnostics. We look forward to further discussion with FDA on how to best implement appropriate HDE policy for diagnostics.

B. Traditional LDTs

We strongly agree that healthcare institutions, such as academic health centers, have a vital role to play and reflect the original intent of enforcement discretion. In such cases, there is common responsibility for patient outcomes that may result from the clinical decisions informed by those device results. Thus, we understand the challenges and believe risk is mitigated to some extent as outlined in the proposal. We recommend, however, that the fourth criteria referenced to lack of automation in lines 808-809 ("without the use of automated instrumentation or software for interpretation") should be removed as automated instrumentation or software for interpretation that has been developed and manufactured under QSR substantially *lowers* the risks associated with such tests. With today's advances, use of this automated instrumentation may make these LDTs more effective and safer for patients than manual processes that are subject to human error.

FDA might wish to consider, however, applying a risk based approach to even traditional LDTs that encourage submissions of high-risk traditional LDTs at some future point in time rather than applying blanket enforcement discretion status for moderate- and high-risk tests. FDA may also wish to conduct a preliminary evaluation of high-risk LDTs, potentially on analytical data alone or minimal clinical data, to determine whether remaining on the market in this manner does not create a patient safety issue. All efforts must be made to strike appropriate balance between patient access to tests and patient safety.

In any case, we would urge careful consideration of any new expansion of this category or distinctions generally that create disparity, introduce unmitigated risk, diffuse accountability, and discourage other developers potentially bringing new safe and effective products to the market. While we support FDA use of continued enforcement discretion for certain FDA requirements in the case of shortages of medically necessary devices as referenced in line 551-553, FDA should better describe what is meant by "or other compelling reasons."

Furthermore, we do not support a move from limited to full enforcement discretion by FDA as minimal premarket and postmarket controls are necessary to support patient access to safe, accurate, and reliable testing.

C. LDTs for Unmet Needs

We wholeheartedly share FDA's concern regarding the need for tests that meet urgent unmet healthcare needs and recognize that LDTs have played a valuable role in this respect. We also concur with FDA that greater flexibility is needed to allow access to diagnostics tests that fulfill unmet needs. The way the draft guidance reads, however, it suggests that the Agency will treat LDTs for unmet needs differently than traditional manufactured diagnostic tests for the same intended use. The answer to this problem is not in creating a new category of LDTs to fill the gap while traditional IVD manufacturers collect the required data. It is in providing a more flexible pathway to bring cleared or approved tests to market for all diagnostic developers.

Other available FDA pathways to promote development of new cleared and approved diagnostic technologies, such as a transitional approach for emerging diagnostics, should be implemented to aid the regulatory process and support good faith efforts by developers of all innovative diagnostic technologies. We note that implementation of a transitional approach for emerging diagnostics is specified in the current user fee agreement and FDA has been working with industry toward such a program. Presently, discussion has been productive and industry looks forward to implementation of a transitional approach as part of the FDA's arsenal of innovative programs to support new diagnostics innovation in the U.S. Diagnostics represent in many ways the future of healthcare. Improved premarket/ postmarket balance will go far to support timely access to emerging diagnostics and the transitional approach described in the user fee agreement is an important step toward spurring development and availability of these new diagnostic technologies. This offers a reasonable pathway to market for tests for unmet need that meet the criteria, regardless of who develops and/or manufactures them, and ensures that those tests have both analytical and clinical validity established while encouraging the development of emerging technologies by sponsors who commit to conduct agreed upon postmarket data collection for their tests.

This type of initiative for all diagnostic tests to support unmet needs safeguards patient safety and encourages continued innovation. This program and other programs can help address unmet needs in a uniform, proactive manner and foster innovation without regard to where a test is developed.

D. *Assessment of Modifications*

As discussed, regulatory requirements should not depend on where a test is developed. Tests present the same risks to patients, irrespective of developer. Changes to tests could significantly affect safety or effectiveness and therefore require a new submission. FDA has

provided guidance (K-97) on the decision making process to determine when a change to a Class II medical device requires a new 510(k) submission. Guidance is also provided for when a PMA supplement is required for a Class III device. When submissions for a change are required, these changes must be cleared or approved by FDA prior to product access. Quality systems processes play an important role in deciding whether a new submission is required. This importantly underscores that innovators must develop and implement a quality system that addresses appropriate practices through the lifecycle of a device from development through the postmarket phase, including how to verify, document, and implement change. FDA seeks to address this quality systems gap in LDT oversight through its risk based framework to equally assure the ongoing safety and effectiveness of LDTs and other IVD tests. The FDA Quality System Regulation's (QSR) requirements provide a solid basis for assuring that LDT modifications are appropriately evaluated via risk management prior to marketing and that the methods and results of evaluation are well documented. In this way, ongoing timely innovation and public health are supported throughout the product lifecycle.

We note lines 1052 to 1055 refer to modifications of another manufacturer's devices. We believe that FDA's intent here is to describe a laboratory's modification of a manufactured diagnostic test, system or software that was cleared or approved by another manufacturer, not by the laboratory itself, and that FDA is not referring to the standard for submitting a change to a laboratory's already cleared or approved device that follows the same standard as described in the previous paragraph (recognizing that some laboratories already have cleared or approved tests). Furthermore, the standard for submitting a modification of a cleared test to FDA is "could significantly affects" safety or effectiveness, not "affects device performance." Similarly, the standard for an approved test would be "could affect" safety or effectiveness. There is some confusion around this topic, and it should be clarified in the guidance.

Lastly, we think it will be helpful to emphasize to laboratories that not all changes trigger submissions to FDA. Furthermore, FDA might consider whether laboratories might be permitted to modify IVDs in specific cases to meet their specific needs (e.g., add specimen types, expand sample stability, new specimen transport media, or other common changes) that can be validated and reviewed during a laboratory's inspection. FDA should ensure a consistent standard for change assessments.

AdvaMedDx appreciates FDA's efforts to develop its thoughtful framework for LDTs. The proposed framework for LDTs is a critical step forward, and we laud the Agency for undertaking this effort. AdvaMedDx has long supported a unified, risk based regulatory approach for all diagnostics, regardless of where they are made, to best support the public health and promote U.S. diagnostics innovation. We welcome finalization of this guidance along with the forthcoming FDA draft guidance on what the Agency considers generally to be Class I, II, or III to help advance the field and support a modernized regulatory approach to diagnostics.

As it moves to finalize the guidance, FDA might consider cross-referencing other relevant guidances in this guidance and any other forthcoming guidances. FDA should also review existing guidance documents to determine if modifications are necessary as a result of this guidance. FDA may also wish to consider development of an LDT labeling guidance as an additional resource to address labeling needs for developers. Alternatively, a section on labeling could be added to the guidance based on appropriate elements of 21 CFR 809.10(b) for this interim period until products are cleared or approved. Such information would particularly help standardize laboratory understanding of cut-off, how cut-offs are achieved, and the data to support the LDTs being offered. Such information could be provided through labeling and perhaps provided in a specific link printed on laboratory reports or the tab report that references an index of links connected to such data for each LDT to support transparency in the interim ramp-up period. This flexibility would likely be appropriate while ensuring robust premarket/postmarket oversight that addresses key recognized public health gaps for LDTs and ensures availability of accurate, truthful information about available tests.

AdvaMedDx appreciates the Agency's development of this helpful guidance. We hope our comments are useful as FDA moves to issue final guidance.

If you have any questions, please do not hesitate to contact me at 202-434-7267 or by email at kcalleja@advamed.org.

Sincerely,

/s/

Khatereh Calleja
Vice President, Technology and Regulatory Affairs

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)

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: October 3, 2014

You should submit comments and suggestions regarding this draft document within 120 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact LDTframework@fda.hhs.gov. For questions regarding this document as applied to devices regulated by CBER, contact the Office of Communication, Outreach and Development in CBER at 1-800-835-4709 or 240-402-7800 or ocod@fda.hhs.gov.

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

Preface

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Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 1739 to identify the guidance you are requesting.

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Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories

Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

A. Introduction

This document describes a risk-based framework for addressing the regulatory oversight of a subset of *in vitro* diagnostic devices[1] (IUDs) 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).

[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 c~~onditions, 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.").

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. 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

[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.

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.

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

[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.

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 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]

[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).

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.

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 IUDs, 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.

[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.

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 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.

[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.

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 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

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

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 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

[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.

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).

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[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.

- 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 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

[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).
[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.

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

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

[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).

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.

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

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]

[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.").

(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 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

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

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 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

[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."

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 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

[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)

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 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

[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)

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

[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

(3) Whether the LDT is comprised only of components and instruments that are legally marketed for clinical use (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 components and instruments legally marketed for clinical use. 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 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,

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.

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 premarket submissions 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).

[34] Companion Diagnostics (also referred to as in vitro companion diagnostic devices or IVD companion diagnostic devices) are in vitro diagnostic devices that provide information that is essential for the safe and effective use of a corresponding therapeutic product. Further information regarding companion diagnostics can be found in the guidance document entitled "In Vitro Companion Diagnostic Devices." http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf

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 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.

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

[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."

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 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

[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.

(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 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:

[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.

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.

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

[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

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

[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.

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.

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)