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FINDING CURES TOGETHER℠

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Food and Drug Administration
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Docket No. FDA-2011-D-0360 for Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

To Whom It May Concern,

On behalf of the American Association for Cancer Research (AACR), the oldest and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication and collaboration, we thank the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the draft guidance on "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)."

The AACR recognizes that the proposed framework is multidimensional and complex. While we appreciate the FDA's proposal for a phased-in approach to regulate LDTs based on the risk posed by the test to the patient, it is clear that there are many outstanding questions and concerns regarding the specifics of the proposal as well as the plan for implementation of the proposed framework. We also acknowledge the FDA's efforts at recognizing the role of academic pathologists in the development of innovative LDTs and at differentiating between academic and commercial LDT vendors by specifying that LDT categories for continued enforcement discretion will be limited to tests developed, manufactured and offered within a single health care system.

We look forward to continuing the dialogue with the FDA to ensure that the final version of the framework will protect patients, instill physician confidence in the validity of the test results, incentivize innovation and advance the practice of personalized or precision medicine. If the concerns expressed in the enclosed document are satisfactorily addressed and additional clarifications are provided, we believe that the proposed framework will adequately reflect the recommendations contained in the AACR's Policy Statement "**Reliable and Effective**

Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care,"[1] which are:

i. Ensuring the safety, reliability and accuracy of diagnostic tests is vital to safeguard patients, advanced personalized medicine and promote innovation.
ii. Implementing a single, strict regulatory pathway through the FDA will help reassure clinicians, patients and the public that the tests used to make treatment decisions, regardless of origin, are safe, accurate and effective.
iii. Having a predictable and reliable regulatory environment is important to encourage an innovative biomedical ecosystem in the United States.

We applaud the FDA's efforts to balance patient safety with promoting product innovation by specifying categories of LDTs that will continue to remain under enforcement discretion including:

i. Traditional LDTs - a category that would encompass the vast majority of currently offered LDTs
ii. LDTs for unmet needs - which will allow laboratories to modify existing tests to meet the unmet needs of the patient populations that they serve and
iii. LDTs for rare diseases - which would allow laboratories to develop and offer tests that are used rarely and therefore, will expose minimal numbers of patients to any risk posed by the test.

The AACR acknowledges that there will be challenges in implementing the new framework for the oversight of LDTs, but believes that the phased-in implementation plan proposed by the FDA, with initial action directed toward high-risk tests, is appropriate and reasonable. We note the FDA's assessment of the number of LDT notifications expected, based on extrapolations from the information provided by New York State, is about 11,000 LDTs for the entire United States in the first year of implementation and about 5% of this number in subsequent years[2]. We note that this number is an estimate of all LDTs and that high-risk LDTs will likely represent a small fraction (1-2%) of the total[3].

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[1] Sawyers and van 't Veer. Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care. *Clinical Cancer Research* 2014; 20: 4978-81. http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Documents/2014-DiagnosticsPolicyStatement.pdf

[2] FR Doc No: 2014-23586; Federal Register Volume 79, Number 192 , October 3, 2014; 59779-59782; http://www.gpo.gov/fdsys/pkg/FR-2014-10-03/html/2014-23586.htm; Accessed January 23, 2015.

[3] Katherine Serrano, Deputy Director, Division of Chemistry and Toxicology Devices, OIR/CDRH, Webinar on "FDA's proposed framework to regulate Laboratory Developed Tests (LDTs)"; slide 7, December 17, 2014; http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/PAGES/REGULATION-OF-LABORATORY-DEVELOPED-TESTS.ASPX; Accessed January 23, 2015.

There are a number of areas of the proposed framework in which additional clarity would be very beneficial, including expansion on the Agency's thinking about risk classification; categories for continued enforcement discretion; harmonization between CMS requirements via CLIA and the FDA requirements for QSR among other concerns. We have elaborated on the AACR's concerns below and made suggestions as appropriate. With these additions, we believe the guidance document will clarify the framework for oversight of LDTs and ensure the availability of reliable and effective diagnostics, regardless of origin, for patients in the United States.

1. Risk categorization and risk-based regulation of LDTs

The draft guidance states that "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 AACR applauds the FDA's proposal to regulate LDTs as medical devices based on the overall risk posed by the test to the patient since this policy is in keeping with the recommendations of our policy statement, Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care [4] "…that all diagnostic tests used to make high-risk treatment decisions, including the tailoring of an individual's cancer treatment regimen, must be FDA-approved to ensure that these diagnostic tests are held to the highest regulatory and approval standards."

We request that the Agency clarify exactly what criteria it will use to assess risk and further, how these will be utilized and applied to categorize tests.

We believe that risk classification should be based on the risk posed to the patient by use of the test rather than the technical or technological complexity of the test. We suggest that the Agency consider the following criteria to assess risk:

i. The risk posed to the patient from performing the test itself. i.e. will the patient be exposed to harm due to an invasive or otherwise risky procedure? The risk posed to the patient due to an erroneous test result and the consequences of that result i.e. does the test have a high false positive or false negative rate? Will the results of the test be used to make a "high-risk" treatment decision like recommending that the patient undergo surgery or recommending the administration of "the wrong therapy"?

[4] Sawyers and van 't Veer. Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care. *Clinical Cancer Research* 2014; 20: 4978-81. http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Documents/2014-DiagnosticsPolicyStatement.pdf

ii. The intended use population for the test. The risk posed by a test varies depending on the context of its use. Thus the "acceptable" risk posed by the exact same test is different when used for a healthy population as opposed to the test being used for a metastatic disease population. We would also like to note that risk tolerance varies by population; thus a population with an unmet need may be willing to tolerate higher risk than a healthy population.

iii. We would like clarification from the Agency on whether risk classification would depend on the context of use of an LDT and whether it would be disease specific? For example, an FDA approved IVD test to detect the BRAF V600E mutation is currently classified as Class III (high -risk) when used as a companion diagnostic to determine whether a metastatic melanoma patient qualifies for treatment with a targeted therapy like vemurafinib. We agree with this classification; however, it is unclear whether the risk classification would remain the same if the intended use of the test was to examine the BRAF V600E status of a patient's tumor for a different purpose (e.g., for observational purposes rather than to determine the course of treatment) or if the test was used to examine the BRAF V600E status in a different disease setting (e.g., early stage disease or in a non-melanoma patient).

iv. We are concerned about risk classification for a single test with multiple intended uses. It would be helpful if the Agency could expand on its thinking about how it intends to classify risk in these cases.

v. The Agency has proposed that LDTs such as prognostic tests which are used to predict a patient's disease risk or the risk of disease recurrence may be classified as Class II (moderate risk) or Class III (high risk) depending on the specific intended uses, claims and limitations of the individual tests.

We request that the Agency explicitly state that tests that are predictive of a patient's germ line risk of cancer (or other diseases) be classified as high risk, if the mitigation of the risk required removal of the organ (e.g., Barrett's esophagus; BRCA 1, 2).

An overarching concern of the AACR is how the Agency will harmonize or synchronize risk categorization with categories of LDTs that merit continued enforcement discretion.

Would an LDT developed to meet an unmet need qualify for enforcement discretion if it also poses high-risk to patients? Or will it be prioritized for PMA application? Given our concerns with ensuring patient safety, we request that the Agency expand on its thinking in this matter.

2. Revision of risk classification

The draft guidance states that, "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. 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."

The AACR applauds the FDA's flexible approach towards risk classification and its acknowledgement that sometimes, diagnostics can be down classified into a lower risk category. Innovations in science and technology are occurring at a rapid pace as is our understanding of the underlying biology of diseases and the natural history of diseases. Therefore, the AACR requests that the Agency periodically review its risk classification of various LDTs such that tests deemed "high risk" may if appropriate be downgraded over time to "moderate" or even "low risk" categories.

3. Continued enforcement discretion for "Traditional LDTs"

The draft guidance states that the 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 LDTs available when FDA began its policy of generally exercising enforcement discretion over LDTs in 1976." The FDA outlines factors that would qualify an LDT to meet this designation as follows:

i. Whether the device is designed, manufactured and used by a single laboratory;
ii. 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; and
iii. Whether the LDT is comprised only of components and instruments that are legally marketed for clinical use (e.g. analyte specific reagents, general purpose reagents, and various classified instruments); and
iv. Whether the LDT is interpreted by qualified laboratory professionals (determined by CLIA), without the use of automated instrumentation or software for interpretation.

The AACR is in agreement with the conditions that have been set forth by the FDA in order for an LDT to meet the designation of a "Traditional LDT". However, it would be helpful if the FDA provided further clarity on what it considers to be a "Traditional LDT" with regards to risk designation. For example, standard human epidermal growth factor receptor 2 (HER2) tests measure if there is a higher than normal number of HER2 genes or receptors on the surface of breast cancer tumor cells. Determination of HER2 status is used to decide if treatment with Herceptin is appropriate. There are FDA approved HER2 testing IVD kits available[5], but there are also several LDTs that offer HER2 testing. Given the importance of HER2 testing to breast cancer treatment decision-making, professional societies (ASCO, CAP) have issued detailed

[5] US FDA approval letter to DAKO for premarket approval application (PMA) supplement for HER2 FISH pharmDXTm Kit. http://www.accessdata.fda.gov/cdrh_docs/pdf4/p040005s005a.pdf; accessed January 23, 2015.

recommendations for how to test for HER2 overexpression, interpret the results and recommend HER2-targeted therapies[6]. In this case, would the FDA exercise enforcement discretion? We request that the Agency use specific examples or case studies such as the above to illustrate its thinking on how risk -categorization and categories for continued enforcement discretion will be interpreted and implemented under the proposed framework.

In the case of a traditional LDT being offered *in lieu* of an FDA approved test as a companion diagnostic, would the LDT be able to use components and instruments that are legally marketed for clinical use, but are not the same as those used in the equivalent FDA approved test? e.g., can the LDT use a different (approved) antibody from the IVD kit?

4. Clarifying the distinction between regulation of tests and practice of medicine

The AACR's primary concern is patient safety. Therefore, we want to ensure that tests offered for patient care meet high standards. The AACR holds that while LDTs should be regulated by the FDA based on the level of risk posed by the test to the patient, the practice of medicine should NOT be regulated or overseen by the Agency. Therefore, it will be crucial to have a clear and precise separation between what will constitute the development and manufacturing of diagnostic tests which will be subject to oversight by the FDA, the actual conduct of the test in a laboratory that is regulated by the Centers for Medicare & Medicaid Services (CMS) through the Clinical Laboratory Improvement Amendments (CLIA) and the practice of medicine which will continue to be the purview of professional medical associations that rely on the expertise of individual medical practitioners. The interpretation of diagnostic test results relies on the judgment of qualified medical personnel and therefore, should continue to be considered as the practice of medicine which is not and should not be subject to regulation by the FDA.

5. Continued enforcement discretion for LDTs for rare diseases

The draft guidance states that the FDA proposes to exercise enforcement discretion for premarket review under the Humanitarian Use Devices (HUD)/Humanitarian Device Exemption (HDE) provisions: "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 (in the United States)." However, "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

[6] Wolff AC, Hammond ME et al, Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update; J Clin Oncol. 2013 Nov 1; 31(31):3997-4013.

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)).”

The AACR agrees that requirements for LDTs for rare diseases should be based on the number of times the test is performed to diagnose or detect the disease and not on incidence or prevalence of the disease itself. There is a subtle but distinct difference between an LDT for a rare disease and rarely performed LDTs. The HUD statute is directed towards rarely used devices similar to the humanitarian use exemption for unapproved drugs. Thus the FDA’s explicit statement that it is proposing this category for enforcement discretion based on the HUD provision indicates that it should be reserved for rarely performed tests. The Agency is permitting use of these LDTs without premarket review with the understanding that the test will be performed rarely and therefore will pose minimal risk to patients.

The AACR asks that the FDA clarify whether this category would apply to an LDT that is performed 4,000 times in the entire country or whether this would apply to an LDT that is performed 4,000 times within a single laboratory.

The AACR would like greater clarity from the Agency on whether it intends this exemption to apply for LDTs for rare diseases or whether it applies to rarely performed LDTs.

For example, how would the Agency exercise enforcement discretion in the case of a test used to detect mutations (including actionable mutations such as BRAF) in patients with a rare disease[7] like multiple myeloma? Multiple myeloma meets the statutory requirements for a rare disease per the Orphan Drug Act[8] where approximately 22,000 new cases are diagnosed each year in the U.S. The reported incidence of the BRAF mutation in this population is 4%[9]. Thus a test used to detect the mutation would potentially identify about 880 patients in the U. S. who might benefit from a BRAF inhibitor.

Our concern is that the risk posed to patients from a rarely performed LDT is very different from the risk to patients from an LDT for a rare disease. For example, the ALK gene rearrangement occurs in about 4-5% of all non-small cell lung cancer (NSCLC) patients[10]. But, in order to detect the mutation, the test itself is performed on all NSCLC patients. Thus, in this case, we would not want the test to be exempt from active FDA oversight.

[7] Rare Disease or Disorder as defined by the Orphan Drug Act, PL, 97-414, 21 CFR section 526.
[8] Ibid.
[9] Chapman MA, Lawrence MS et al, Initial genome sequencing and analysis of multiple myeloma, *Nature*. 2011 Mar 24;471(7339):467-72
[10] Chia PL, Mitchell P, Dobrovic A, John T, Prevalence and natural history of ALK positive non-small-cell lung cancer and the clinical impact of targeted therapy with ALK inhibitors, *Clin Epidemiol*. 2014 Nov 20; 6:423-32.

Additionally, we would not want an LDT, such as an oncology panel, that incorporates a rare variant to be able to claim this exemption if it is performed for greater than 4,000 people annually, even if the rare variant itself is detected less than 4,000 times per year. It would be helpful if FDA provided further clarification on how a laboratory (especially a small local laboratory) is expected to know national rates of testing for a specific test? If the FDA intends to notify labs of all tests that are performed on less than 4,000 people each year, then the Agency should clarify the process for doing so.

What happens if an LDT is designated for rare diseases and the annual number of individuals tested exceeds 4,000 in the U.S.? How will the laboratory be notified? How long will the laboratory have in order to file a Premarket Application (PMA) or 510(k)?

Is there a limit to the number of LDTs that can get this designation for a specific rare disease? For example, would all LDTs used to diagnose a certain rare disease be considered a HUD? Will the exemption be based on the technology employed even if two different tests are ultimately used for the same purpose? For example, if one lab uses an IHC-based test and another employs a PCR-based test for the same purpose, will both tests be eligible for this designation? Will the 4,000 tests per year be based on the type of technology used? For example, if a PCR-based test is used 3,000 times to diagnose a disease and an IHC test is used 2,000 times to diagnose the same disease, their combined use exceeds the 4,000 cutoff, but individually they would not meet the threshold.

The FDA cannot approve a Humanitarian Device Exemption (HDE) for HUD once a comparable device is marketed through either a PMA or approved 510 (k)[11]. Would the same be true for LDTs for rare diseases? What would happen to LDTs already under this designation? How long would they have to come into compliance with premarket requirements?

Since the FDA will be exercising enforcement discretion with regards to premarket review for LDTs for rare diseases, would those tests that are exempt from premarket review requirements be required to collect evidence of clinical validity in the postmarket setting?

The FDA states that enforcement discretion for premarket review and Quality Systems (QS) regulation for rare diseases LDTs derives from the HUD statute. However, the HUD statute requires tests to be in compliance with Quality Systems Regulations (QSR). Does this mean that LDTs for rare diseases will have to be in compliance with QSR? If not, would applying this consideration for rare diseases to other IVDs (which the FDA is considering) supersede HDE requirements, therefore allowing IVDs for rare disease to no longer be subject to QSR? If LDTs

[11] U.S. Food and Drug Administration. Humanitarian Device Exemption (HDE) Regulation: Questions and Answers. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110203.pdf Accessed on January 4th, 2015

for rare diseases must comply with QSR, can the Agency explain its explicit exemption of traditional LDTs and LDTs for unmet needs from meeting the same standards?

The AACR would also like to note that the FDA has the authority to rapidly approve tests under its Emergency Use Authorization (EUA) provisions under exigent circumstances. We believe that the EUA policy works well for IVDs including LDTs that are needed for emergency needs as evidenced by the recent authorizations of tests to detect Ebola[12].

If an LDT meets the requirements for a rarely performed test we suggest that it may be appropriate for the Agency to relax the condition that the test must be designed, manufactured and used within a single laboratory to allow for greater patient access to the test.

For example, a state public health laboratory may be allowed to offer a rarely used test during a disease outbreak. In fact, it may be prudent to allow a laboratory with expertise in a rarely performed test to offer the test widely rather than have the rarely performed test be offered by laboratories that may not necessarily have the requisite expertise to perform the test.

6. Continued enforcement discretion for LDTs for Unmet Needs

The AACR supports a framework that will balance patient safety with promoting product innovation. Therefore, we applaud the FDA's efforts to promote innovation by lessening the premarket requirements for LDTs for which there are no existing FDA approved or cleared tests. However, we are concerned that some LDTs that may qualify for enforcement discretion as "LDTs for Unmet Needs" may also pose a high -risk to patients due to their lack of either pre or post market review for clinical validity. The draft guidance states that LDTs for unmet needs can use Research Use Only (RUO) reagents or instruments. Further, enforcement discretion will extend to the use of software in the case of LDTs for unmet needs. We welcome this allowance by the FDA as we believe this will allow labs to innovate and offer new tests as well as offer improvements over existing tests.

Given the lack of premarket review for LDTs for unmet needs and the fact that some of these tests may pose high -risk to patients, we suggest that minimal safety and/or adverse event (AE) data collection may be appropriate once the test is offered to patients.

We suggest that the Agency define what minimal safety/AE data would be appropriate to record and further that appropriate mechanisms, such as registries, to record and collate these data would serve to ensure patient safety while minimizing the burden on laboratories. If appropriate

[12] U.S. Food and Drug Administration. 2014 Ebola Virus Emergency Use Authorizations. http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm Accessed on January 7th, 2015

based on the specific test and its intended use, registries could be expanded to include efficacy data as well.

It would be helpful if the FDA defined what level of specificity of intended use the Agency considers to be acceptable for claiming "LDT for Unmet Needs." For example, if a lab modifies an FDA approved universal cancer panel or develops an "equivalent panel" with:

i. The addition of codons/exons/genes
ii. Modification of the panel such that its intended use population is now for a specific type of cancer patient (e.g. lung cancer)
iii. Modifications of the sample type (blood versus solid tissue)
iv. Utilizing a different analytical software package

Could each or all of the above modifications suffice to meet a claim for "LDT for Unmet Needs"?

The draft states that "Modifications to FDA cleared /approved devices" include modifications that affect "intended use." Given that labs can modify an IVD to develop a test for unmet need, can FDA clarify the difference between "modification to an existing IVD" versus developing an "unmet need" test? How can a laboratory "apply" for "unmet need" exemption? Can the FDA deny a petition for "unmet need"?

7. Adverse Event Reporting

The draft guidance states that FDA "requires the manufacturer of a medical device to submit reports to 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."

The AACR seeks clarification from the Agency on what exactly would constitute an "Adverse Event" (AE) for an LDT?

Would incorrect test result reporting constitute an AE, even in cases where the test itself was performed according to accepted protocols? Would test error rates (false positives/negatives) need to be captured as part of AE reporting?

We would like greater clarity on the responsibility of the laboratory to track AEs.

What specific information should be collected? What "events" should be tracked by the laboratory and how should this information be collated, stored and reported to the Agency? For example, in cases where a laboratory uses approved reagents to assemble and perform a test, if a laboratory notices quality problems with manufacturer supplied reagents that has downstream impacts on the outcome of test or affects test performance, is it the responsibility of the laboratory or the manufacturer to inform the Agency?

It would be helpful if the FDA clarifies what it considers to be a serious injury and what it does not. For example, if a patient is subjected to costly, unnecessary, non-invasive testing due to an erroneous result from an LDT, would this constitute a serious injury?

8. Restricting use of certain LDTs within a healthcare facility

The draft guidance proposes that one of the conditions that should be met for enforcement discretion of an LDT as a "Traditional LDT" or as an "LDT for Unmet Needs" is: "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."

The AACR applauds the FDA's efforts in recognizing the shared accountability of laboratories within a hospital system for patient safety and believes that it is an appropriate approach to mitigating risks to patients. Likewise, the AACR also believes that the above provision is necessary to offset the lack of accountability of laboratories outside the hospital system to patient safety if an error in testing were to occur.

9. Labeling

In vitro diagnostics are subject to labeling regulations as outlined in 21 CFR 809.10. There has been concern as to what constitutes a "label" with regards to an LDT, since they do not consist as a physically packaged unit like other IVDs.

The AACR offers that any and all materials used to market to physicians as well as those that are delivered (test reports) to the ordering physician should comprise the label and therefore should contain information such as:

i. marketed or designed intended use[13],
ii. any disclaimers or caveats associated with the test,

[13] U.S. Food and Drug Administration. Guidance for Industry: General/Specific Intended Use. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073945.pdf Accessed on January 7th, 2015

iii. potential adverse events,
iv. whether the reagents, equipment, and software components of the test are FDA approved,
v. whether the test itself is FDA approved or cleared (or meets one of the categories for enforcement discretion),
vi. other requirements detailed in 21 CFR 809.10.

While likely included with the label, the interpretation of the results by a qualified individual (e.g., pathologist) constitutes the practice of medicine and therefore should not be regulated by the FDA.

10. Notification of LDTs

The AACR believes that it is acceptable for a laboratory network to offer a single notification provided that the LDT is performed to the same specifications (with the same reagents, protocols, etc.) within all of its sites, and each laboratory site is independently inspected and certified by CLIA. The AACR believes that in order to ensure consistency of test quality and performance and to mitigate patient risk, the FDA should enforce notification by laboratories for all of their LDTs. The AACR believes that it is appropriate for the FDA to exercise enforcement discretion regarding subsequent registration and listing requirements.

The draft guidance states that, "FDA intends to exercise enforcement discretion for applicable premarket review requirements and quality systems requirements (QSR), but enforce other applicable regulatory requirements (notification, general controls, and adverse event reporting) for "LDTs for rare diseases", "Traditional LDTs", and "LDTs for Unmet Needs".

It would be helpful if the FDA could provide further clarification on how laboratories are expected to know if their LDTs fall under the above categories for continued enforcement discretion.

Would laboratories have to specifically apply for exemption of active FDA oversight upon notification of their traditional or rare disease or unmet need LDTs to the FDA, and can the Agency deny applications for exemption of active oversight?

The draft guidance proposes that LDTs for rare disease and LDTs for unmet need will not be subject to premarket review. Can the FDA issue a recall if the test is subsequently found to have serious adverse events? If so, can the Agency detail the steps it will take to do so?

The draft guidance states: "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; b) LDTs with the same intended use as an FDA-approved Class III medical device;"

It would be helpful if the FDA could clarify how it proposes to inform laboratories that their LDTs are subject to the initial enforcement after notification – i.e., inform those laboratories that are offering the highest risk LDTs.

11. "Significant modifications" to existing tests

The draft guidance states that the FDA must be notified if "significant" modifications are made to an existing LDT: "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."

Laboratories are constantly modifying their LDTs. We encourage responsible modification of existing tests since this leads to innovative test development and/or improvement of existing tests. Thus it would be helpful if the Agency could elaborate or detail the various categories of changes and specify which changes would merit notification and which changes would not. It would be helpful for the FDA to clarify what changes it considers to be insignificant, and therefore do not warrant a new LDT notification. For example, if an LDT is developed for use with fresh tissue from a surgical resection as the appropriate sample and subsequently the laboratory modifies it for fresh tissue from punch biopsies; would this sample change be considered significant by the FDA?

The Agency gives the example of a change in sample type (saliva versus whole blood). Would a test developed for whole blood be considered to be significantly modified if the test was modified to use serum instead? In other words are there any instances where a change in sample type would NOT constitute "significant" modification?

If a laboratory has already notified FDA of an LDT, and subsequently makes a significant modification after the 6-month deadline but before the agency begins enforcing premarket requirements for that LDT category, will the laboratory be allowed to notify the Agency of said modification? Could the Agency detail the processes and procedures to be followed? Would the laboratory be allowed to market the modified LDT after notification? Besides notifying the Agency, are there other requirements for laboratories that make "significant changes" to cleared LDTs, before offering/ marketing the test? How will the Agency notify the laboratory of any premarket requirements before they can market or offer their modified LDT?

12. Evidence requirements for clinical validity of LDTs

The draft guidance states that, "FDA expects that for many LDTs, clinical validity has already been established in the 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."

The AACR welcomes the Agency's willingness to accept evidence other than the data gathered via a clinical trial to establish the clinical validity of a test. It would be helpful if the FDA could elaborate on what it would consider to be appropriate in assessing clinical validity from the scientific literature? For example, would non-human studies involving the LDT be appropriate? Would practice guidelines recommending the use of certain tests be appropriate? If the LDT is a multigene panel, would the laboratory be required to submit information for all of the genes included in the panel?

The draft guidance states that, "Devices would remain on the market during review and FDA's consideration of applications." If the FDA determines that further clinical investigation is needed to determine analytical or clinical validity, would the LDT still be allowed to remain on the market during the additional investigations?

13. Harmonization between FDA and CMS

The AACR requests that the FDA make every effort to align with the Centers for Medicare & Medicaid Services (CMS) to harmonize both CLIA and QSR inspection requirements[14].

AACR's commitment to facilitating a multistakeholder dialogue

We are acutely aware of the widely differing opinions on the role and scope of the FDA's oversight of LDTs, particularly in the pathology community, many of whom are members of the AACR and are opposed to the proposed framework. However, after much deliberation and feedback, we have made the decision to participate in a constructive dialogue with the Agency and work hard to resolve the important issues described in this document. It is the AACR's responsibility to represent its members and to take into consideration their diverse opinions on matters such as the FDA's proposed framework for regulatory oversight of LDTs. Therefore, as this is the beginning of a dialogue with the FDA to ensure the effectiveness of the proposed framework, we have put forth comments that are representative of the majority of our membership.

[14] Centers for Medicare & Medicaid Services. LDT and CLIA FAQs. http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf Accessed on January 12th, 2015

As an organization that marshals the full spectrum of expertise of the cancer research community to accelerate progress in the prevention, etiology, diagnosis, and treatment of cancer, we believe it is incumbent upon the AACR to advocate for a framework that protects patients, instills physician confidence in the validity of the test results, incentivizes innovation and advances the practice of personalized or precision medicine.

We would also like to note that we are continuing to facilitate a dialogue on this framework by hosting a special session at the upcoming 2015 AACR Annual Meeting on April 21, 2015, from 5:00 – 6:30 p.m. at the Convention Center in Philadelphia, PA. This session will encourage substantial discussion between FDA and AACR members and other attendees on this significant issue.

In conclusion, the AACR commends the FDA for its commitment and proactivity in regard to its important proposal. We would be pleased to offer the AACR's broad scientific and clinical expertise to the FDA as the Agency further considers revisions to the draft guidance on "**Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs).**" If you have any questions about the above comments or require follow up, please contact any of the signatories or Rasika Kalamegham, PhD, Director, Regulatory Science and Policy, AACR at 267-765-1029 or rasika.kalamegham@aacr.org.

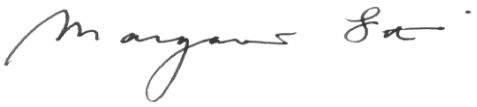
Sincerely,

Carlos L. Arteaga, MD

President

Charles L. Sawyers, MD

Immediate Past President



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