

Discussion Paper on Laboratory Developed Tests (LDTs) January 13, 2017

The Food and Drug Administration (FDA) recently announced that we would not issue a final guidance on the oversight of laboratory developed tests (LDTs) at the request of various stakeholders to allow for further public discussion on an appropriate oversight approach, and to give our congressional authorizing committees the opportunity to develop a legislative solution.

In gathering feedback on the LDT draft guidances issued in 2014, we continuously engaged with interested stakeholders, including those groups that authored alternative proposals. We analyzed more than 300 sets of comments on the draft guidances and discussion from a subsequent public workshop held in 2015 as well as engaged in many meetings and conferences with various stakeholders. Because we did not issue a final guidance, all that is currently available to the public are the individual comments on the 2014 draft guidances submitted to the federal docket and the transcript of the workshop. In the absence of issuing final guidance and at the request of stakeholders, we feel it is our responsibility to share our synthesis of all the feedback we have received, with the hope that it advances public discussion on future LDT oversight.

As part of this synthesis we have included a possible approach to LDT oversight, which is based on the extensive, and often conflicting, feedback we received from a broad range of stakeholders. This possible approach is intended only to respond to stakeholder feedback and attempt to balance patient protection with continued access and innovation. Given the wide range of perspectives on this issue, no approach is likely to fully satisfy all stakeholders.

The synthesis does not represent the formal position of FDA, nor is it enforceable. We hope to simply advance the public discussion by providing a possible approach to spur further dialogue. This document does not represent a final version of the LDT draft guidance documents that were published in 2014.

INTRODUCTION

Patients and health care providers need accurate, reliable, and clinically valid tests to make good health care decisions. Inaccurate or false test results, or accurate measurements with an invalid claim regarding the test results' relationship to a disease, can lead to substantial patient harm. LDTs play an increasingly important role in the provision of high-quality health care and many laboratories perform good validation of their LDTs and provide high-quality, professional management of their operations. However, currently, patients and providers cannot uniformly rely on all tests offered for clinical use as some are not subject to active premarket oversight to ensure they provide accurate measurements and valid claims. Furthermore, CMS' evaluation of clinical utility, as part of a coverage determination, would typically follow from FDA review of analytical and clinical validity.

While excessive oversight can discourage innovation, inadequate and inconsistent oversight in which different test developers are treated differently can also discourage innovation by making it difficult for high-quality test developers to compete with poorer performing counterparts. Limited investment and health care funding may be expended on faulty tests rather than focused on tests that lead to improved care. When patients and providers discover that results they relied upon to make treatment and/or diagnostic decisions were inaccurate, their confidence in laboratory testing may be compromised. In a recent example, ovarian cancer screening tests offered to asymptomatic patients were shown not to work only after patients unnecessarily underwent major surgeries with significant recovery and side effects.¹

Without more active oversight, similarly problematic LDTs will continue to be offered in the future. FDA^{2,3,4,5,6,7,8} and others^{9,10,11,12,13,14,15} have consistently asserted that there is a public health need for greater oversight of LDTs. Appropriately tailored oversight can facilitate the development of analytically and clinically valid tests and the generation of the evidence health care providers and patients need to make well-informed decisions.

FDA proposed a comprehensive LDT policy¹⁶ in 2014 that was intended to protect patients, promote innovation, and provide clarity regarding FDA oversight of LDTs. This proposal and the ensuing public workshop¹⁷ prompted extensive comments and discussions among laboratories, health care providers, patients, conventional in vitro diagnostic (IVD) manufacturers, government agencies, and Congress. Based on the extensive community engagement over the last two years, the positions of many groups, including FDA, have evolved.

There is a growing consensus that additional oversight of LDTs is necessary, as reflected in several recent oversight proposals put forward by some organizations representing laboratories and the IVD industry.^{18,19,20,21,22} Although these proposals differ in some respects, they generally share the following features:

- A risk-based approach to oversight;
- Independent premarket review for certain tests and for some modified tests;
- A focus on analytical and clinical validity as the basis for test approval;
- Risk classification activities;
- Adverse event reporting;
- Exemption of certain categories of tests from premarket review;
- A robust laboratory quality system;
- “Grandfathering” for tests available prior to a specific date; and,
- Public availability of test performance information.

These proposals differ with respect to which federal agency would be responsible for any additional oversight: FDA, the Clinical Laboratory Improvement Amendments (CLIA) program, which is overseen by the Centers for Medicare and Medicaid Services (CMS), or a hybrid model under which FDA and CMS engage in complementary, non-duplicative oversight have been proposed.

Based on the feedback we have received, the complementary approach in some form is supported by the broadest array of stakeholders, including some members of the laboratory community. This approach may best streamline effective oversight by taking advantage of each federal agency’s existing structure and strengths, including FDA’s experience in premarket review of diagnostics and its deep knowledge of clinical research methodology pertinent to clinical validity. Such an approach could foster innovation and advance patient access to cutting-edge, high-quality, accurate, and clinically valid tests as long as it is also reasonable, appropriately tailored, and least burdensome.

On the other hand, a CMS-only framework for additional oversight could create inconsistencies in the marketplace. For example, under some proposals the same test would be regulated by FDA if made by a conventional manufacturer but by CMS if made by a laboratory. This would be a developer-based framework, rather than a risk-based framework, as the oversight authority would be determined by who made the test rather than on what the test is intended to do and the risks it presents to patients. This could create jurisdictional challenges as the agency responsible for oversight could continually change over the course of its application to clinical care. For example, a test made by a conventional IVD manufacturer

would be regulated by FDA initially. If a laboratory made a significant modification to that test, it would then be regulated by CMS. If the original manufacturer then made another significant modification, the modification would be regulated by FDA. This would be confusing, at best.

In addition, it could be difficult for a CMS-only LDT framework to duplicate FDA capabilities (and FDA's 40-year experience in assuring the analytical and clinical validity of tests) as CMS's oversight of laboratories through CLIA is fundamentally different from FDA's oversight of the tests themselves.

Adapting CLIA to enable CMS to provide the kind of effective oversight of LDTs that is needed to ensure that they are accurate, reliable, and clinically valid would require a significant change in the nature of what the agency does, rather than minor modifications as some have suggested. By its very nature, a CMS-only framework for LDTs could create costly federal redundancies and inefficiencies.

The approach described below is based on a synthesis of the public feedback FDA received. In gathering feedback, FDA engaged with interested stakeholders, including those groups that authored alternative proposals, and analyzed more than 300 sets of comments on the 2014 draft guidance and a subsequent public workshop held in in 2015 as well as engaged in many meetings and conferences with various stakeholders.

Generally, many patient groups, the oncology community, consumer groups, conventional IVD manufacturers, pharmaceutical companies, and public and private health insurers supported FDA's risk-based, phased-in approach to LDT oversight. The laboratory community, including hospital laboratories, academic medical centers, and laboratory professional societies, generally expressed opposition to FDA's proposed LDT oversight approach. Many who supported FDA oversight expressed concerns about current gaps in LDT oversight and some were concerned that many LDTs are being marketed without any independent review of clinical validity, potentially harming patients and wasting health care dollars. Many of those who opposed FDA oversight expressed concerns about slowed innovation, increased costs, and reduced patient access. The comments FDA received included both general views on LDT oversight as well as more specific comments on the details of the draft guidances. Based on this extensive feedback, several alternatives to what FDA proposed in 2014 should be considered, including:

- Exempting LDTs already on the market from all FDA oversight except for adverse event and malfunction reporting ("grandfathering"), and exempting traditional LDTs (see below) and LDTs for public health surveillance from all oversight;
- Not adopting proposals requesting laboratories to notify FDA of their LDTs on the market because FDA generally would no longer need to classify LDTs currently on the market as the result of "grandfathering";
- Providing additional time before FDA would begin actively overseeing certain regulatory requirements; and
- Shortening the overall phased-in timeframe.

The possible approach described below incorporates these and other changes with the intent to respond to stakeholder feedback and to appropriately balance patient protection with continued access and innovation, with the caveat that given the wide range of perspectives, no approach is likely to fully satisfy all stakeholders. This approach addresses only the LDTs that are designed, manufactured, and used in a CLIA certified lab; many elements would not be appropriate for conventional IVD kits.

FOCUSED OVERSIGHT

Based on the feedback received, a *prospective* oversight framework that focuses on new and significantly modified high and moderate risk LDTs would best serve the public health and advance laboratory medicine. Under such an approach, as further explained below, previously marketed LDTs would not be expected to comply with most or all FDA regulatory requirements, including premarket review, quality systems, and registration and listing, unless necessary to protect the public health. Some refer to this concept as “grandfathering.”

Additionally, new and significantly modified LDTs in the following categories would not be expected to comply with premarket review, quality systems, and registration and listing requirements unless necessary to protect the public health:

- Low risk LDTs;
- LDTs for rare diseases;
- Traditional LDTs (i.e., tests that use components that are legally marketed for clinical use²³ and whose output is the result of manual interpretation by a qualified laboratory professional, without the use of automated instrumentation or software for intermediate or final interpretation);
- LDTs intended solely for public health surveillance (i.e., intended solely for use on systematically collected samples for analysis and interpretation of health data that are essential to the planning, implementation and evaluation of public health practice, which is closely integrated with the dissemination of these data to public health officials and linked to disease prevention and control²⁴);
- LDTs used in CLIA-certified, high-complexity histocompatibility labs to perform allele typing, antibody screening and monitoring, or crossmatching in connection with organ, stem cell, and tissue transplantation; and
- LDTs intended solely for forensic use.

To protect patients from tests that could lead to harm, the agency would retain its ability to enforce premarket review, quality systems, and other applicable requirements for any LDT, including those listed above, if the agency identified one or more of the following, taking into account all available evidence:

- The LDT is not analytically and clinically valid or there is an absence of sufficient data to support its analytical and clinical validity;
- The manufacturer of an LDT has engaged in deceptive promotion; or
- There is a reasonable probability that the LDT will cause death or serious adverse health consequences.

RISK-BASED, PHASED-IN OVERSIGHT

Consistent with proposals from other stakeholders, premarket review of new and significantly modified LDTs could be phased in over four years, rather than the nine years proposed in FDA’s 2014 draft guidance, because LDTs currently on the market generally would be “grandfathered” thereby reducing the overall workload on laboratories and FDA. The agency could focus first on the tests for which the consequences of a false result are known to have the highest risk to the patient, with an additional two years to meet applicable quality systems requirements. The following risk-based approach to phase-in of oversight could be adopted:

- Year One: Serious adverse event and malfunction reporting for all LDTs except: traditional LDTs, LDTs intended solely for public health surveillance, certain stem cell/tissue/organ transplantation LDTs, and LDTs intended solely for forensic use.
- Year Two: Premarket review for new/modified LDTs with the same intended use as an IVD approved under a PMA (i.e., tests that have already been identified as high risk by FDA).
- Year Three: Premarket review for new/modified LDTs with the same intended use as a Class II device type subject to 510(k) clearance (i.e., tests that have already been identified as moderate risk by FDA).
- Year Four: Premarket review for new/modified LDTs that do not fall into the above categories.

To ensure patient access to existing tests is not disrupted, those tests that are introduced between the effective date of such framework and their phase-in date could continue to be offered for clinical use during the period of premarket review. Because FDA Quality System requirements would likely be a new activity for laboratories, and to help foster innovation, such tests would also have an additional two years before having to meet quality system requirements, as described below. In addition, because tests could be offered for clinical use prior to FDA's readiness to review them, registration and listing would occur at the time an LDT receives marketing authorization.

In its 2014 draft guidances and related statements, FDA said that more flexibility is important for new LDTs that address unmet needs in order to promote innovation and patient access to tests leveraging new scientific findings. Stakeholders echoed this belief in their comments to FDA, but expressed some concerns about the unmet needs policy as written in the 2014 draft guidance because it did not provide assurances that these tests for which there is the least practical experience are analytically and clinically valid. On the other hand, some stakeholders commented that the scope of LDTs for unmet needs should be broadened to include tests not made by a health care system laboratory, to promote fair access to such tests. As such, a new approach for a more broadly defined category of LDTs for unmet needs (i.e., any test designed, manufactured, and used in a single laboratory for which there is no FDA cleared or approved alternative at the time the LDT enters the market) should be considered. For example, to promote innovation and patient access, laboratories could have up to 90 days after offering an LDT for an unmet need to send a premarket submission to FDA or an accredited third party reviewer, when applicable, and could continue to offer the test during FDA's or the third party's review (*see* Third Party Review section below).

EVIDENCE STANDARDS

Traditionally, FDA focuses on analytical and clinical validity as the practical bases for test marketing authorization; specifically, FDA evaluates whether there is a reasonable assurance of analytical and clinical validity for the test. CMS evaluates whether there is clinical utility for the specific test. Independent review of analytical and clinical validity by FDA, which today is generally only enforced for high and moderate risk tests made by conventional IVD manufacturers, allows for an unbiased check on the quality of the evidence and ensures that it is sufficient to establish that the test works as claimed or intended. Laboratories that already conduct proper validation should not experience new costs for validating their tests to support marketing authorization.

FDA's premarket review would be complementary to, and not duplicative of, CMS's postmarket oversight of laboratory operational processes as well as its determinations of clinical utility. CMS coverage determinations of clinical utility measures the ability of the test to impact clinically meaningful health outcomes, such as mortality or morbidity, through the adoption of efficacious treatments. CMS's

oversight through the CLIA program is designed to confirm that a lab assesses analytical validity, but does not confirm whether it had results from an analytical validity assessment that were sufficient to support the claimed intended use of the test. Also, while CMS assesses the clinical utility of a test, evaluation of clinical validity is critical to ensure that providers and patients have access to tests that improve care. Independent premarket review of a test's clinical validity is becoming increasingly important to providing high-quality health care because labs and conventional IVD manufacturers are attempting to rapidly translate novel scientific findings/hypotheses to clinical care before data supporting clinical significance is made publicly available. This means LDTs that have not undergone appropriate premarket review may still be putting patients at considerable risk.

Because CMS requires that laboratories establish the performance characteristics of their tests, we anticipate that laboratories that conduct appropriate evaluations would not have to collect additional data to demonstrate analytical validity for FDA clearance or approval. Additionally, in situations where there is a robust and appropriate proficiency testing program, accepted reference and review standards or a certification program for a specific test, such as the National Glycohemoglobin Standardization Program (NGSP) or the Cholesterol Reference Method Laboratory Network (CRMLN), FDA would work collaboratively with health care professional, laboratory, and conventional IVD manufacturer communities, as well as other stakeholders, to determine how such programs could be leveraged to reduce the burden of premarket review. This could significantly expedite premarket review. If the law is changed, availability of such programs and standards may eliminate the need for premarket review of analytical validity through FDA recognition of certain review standards developed by such programs (*see* the Clinical Collaboratives section below).

Clinical validity, especially of established tests, can often be supported by literature, well-curated databases, or other appropriate sources that meet the valid scientific evidence standard. Accordingly, once clinical validity has been well established, laboratories with subsequent tests generally could, in accordance with applicable regulations, leverage such evidence of clinical validity when factors such as indications for use, technology, and standardization are the same, without the need to re-demonstrate clinical validity. This also could apply to tests whose methods are shown to perform similarly to the methods used in the studies reported in the literature.

Controls and oversight mechanisms in place under CMS and the Occupational Safety and Health Administration generally address potential safety issues with LDTs that are unrelated to performance, including the potential for direct harm through transmission of infectious disease, or physical harms to users. However, if any component of an LDT were to come in direct contact with a patient, as with some conventional IVD kits, additional evaluation of safety should be performed.

THIRD PARTY REVIEW

FDA would expand its third party premarket review program to include eligible LDTs. FDA has already begun working towards this goal by exploring opportunities to coordinate with and leverage existing programs, such as New York State's Clinical Laboratory Evaluation Program and the programs run by organizations approved by CLIA to accredit laboratories. Many LDTs that have not been FDA cleared or approved require premarket review by the New York State Department of Health's (NYSDOH) Clinical Laboratory Evaluation Program (CLEP) if the test is performed in New York State or the sample is from New York State. In fact, NYSDOH has reviewed more than 11,000 new and modified LDTs over a ten-year period, which we understand may account for around 50 percent of new and modified LDTs. Many laboratories are therefore well accustomed to complying with premarket review requirements through this program. Arguably, this type of premarket oversight, which is currently provided by NYS for some tests,

is important for *all* high risk and moderate risk laboratory tests so that all patients across the country – not just those in NYS – can be assured they are receiving a test that is analytically and clinically valid. (Note that NYSDOH and FDA are not duplicative. Tests that are reviewed by FDA would not need NYSDOH review because NYS recognizes FDA review. FDA is exploring accepting NYSDOH review in lieu of its own.)

CLINICAL COLLABORATIVES

FDA would expand its collaborative work with the health care professional, laboratory, and conventional IVD manufacturer communities, as well as other stakeholders, to develop measurement and review standards for analytical validity for tests where feasible and beneficial; crowdsource evidence to demonstrate clinical validity for specific types of tests; and develop, for FDA recognition, standards for use in determining clinical validity for specific types of tests. FDA would expand its use of such clinical collaboratives by leveraging, to the extent appropriate, existing entities such as health care professional organizations. By applying such analytical and/or clinical validity standards, FDA and accredited third party reviewers could rely in part or wholly on the interpretation made by the clinical collaborative. FDA oversight would help ensure the quality and consistency of analytical and clinical validity determinations based on valid scientific evidence, while streamlining time and cost, thereby enabling regulatory decisions to be made in near real time when FDA, in collaboration with the clinical community, believes the evidence is adequate to support the intended use of the test.

TRANSPARENCY

Evidence of the analytical and clinical validity of all LDTs would be made publicly available, such as through publication in a journal, on the laboratory's website, or elsewhere, since understanding the test performance and how it was derived is crucial to understanding how to use the results.

For those tests that would be reviewed by FDA, the agency would publish its review memorandum containing such information. For those that are not reviewed by FDA, laboratories should consider making such information public. FDA would work collaboratively with the health care professional, laboratory, conventional IVD manufacturer, and patient communities, as well as other stakeholders, to develop shared and reasonable expectations for the content and format of such information to best meet the needs of health care professionals and patients to make well-informed decisions.

It would continue to be appropriate for laboratories, at their discretion, to respond to specific requests from treating physicians and other health care professionals to run a particular test that is not FDA reviewed for the requested intended use for the sole purpose of diagnosing or treating a specific individual patient.

MODIFICATIONS

Regulatory policy should be sufficiently flexible so as to enable laboratories to make modifications without undue burden, while still providing assurances to users that the modifications do not affect the underlying test's ability to perform as intended. FDA would encourage laboratories to submit prospective change protocols in their premarket submissions that outline specific types of anticipated changes, the procedures that will be followed to implement them, and the criteria that will be met prior to implementation.

Following marketing authorization, modifications made in accordance with the change protocol, including the specific procedures and acceptance criteria, could be made without the need for a new submission. For this reason, premarket review of modifications to an already marketed test (including a “grandfathered” LDT or another manufacturer’s IVD kit) would be limited to only those modifications that significantly change performance specifications or intended use of the test and are not made in accordance with the test’s approved change protocols, including approved verification and validation methods. The systematic use of the change-protocol approach would narrow the circumstances under which a test modification would be subject to FDA review. Therefore, it would be important that laboratories keep good documentation of the changes they make and how those changes conform to the laboratory’s change protocols.

LEVERAGING CMS/CLIA: QUALITY SYSTEM REQUIREMENTS FOR LDTs

In 2015, FDA established an Interagency Task Force on LDT Quality Requirements with CMS, the Center for Disease Control and Prevention, and the National Institutes of Health to evaluate current quality system (QS) requirements and assess where existing quality controls are adequate as well as whether and where additional oversight is warranted to address LDT development activities. Through the Task Force, FDA met with all seven accreditation organizations (AO) approved by CMS to conduct CLIA survey inspections, as well as the two state departments of health approved by CMS for exemption from CLIA program requirements, to better understand how each program operates and the extent of additional oversight their certifications provide beyond CLIA requirements. Most of these organizations’ evaluations go beyond the minimum CLIA requirements, but no organization or any combination of organizations evaluate all relevant elements of LDT development addressed by FDA’s QS regulation. Furthermore, laboratories are not required to select an AO for the purpose of CLIA accreditation; they may register with the CLIA program and be surveyed by CMS state inspectors who do not evaluate any elements beyond CLIA.

The Task Force confirmed that FDA and CMS oversight is different and complementary. FDA oversight focuses on individual test performance, while CMS oversight focuses on administering the CLIA program of certifying laboratory operations. In addition, CMS reviews LDTs for coverage determinations with a focus on clinical utility – the ability of the test to impact clinically meaningful health outcomes, such as mortality or morbidity, through changes in clinical management and the adoption of efficacious treatments based upon the results of the test. To supplement the Task Force analysis, FDA visited a wide variety of laboratories running LDTs, including large reference labs, academic labs, and specialized single-technology labs. Many laboratories have quality management systems that go beyond CLIA requirements and some carry accreditations to higher quality standards, such as the College of American Pathologists (CAP), NYSDOH and the International Organization for Standardization (ISO). These visits allowed FDA to better appreciate that good professional management of laboratory operations, as required under CLIA and performed routinely in laboratories across the country, can address many quality-related issues pertaining to the development, maintenance, and modification of LDTs. Of note, as well, FDA’s current QS requirements are not a panacea to prevent quality-related problems. Quality-related problems may occur with FDA-regulated tests even when all QS requirements are met. However, if these requirements are met such problems should be detected and appropriately addressed in a timely manner.

On the other hand, not all quality-related issues are addressed by CLIA. Neither CLIA nor the programs that accredit to higher standards ensure quality in the design, development, and manufacturing activities comparable to that of the FDA QS regulation. Notably missing from all other accreditation standards are

robust design controls, which are critical to the quality of tests and for which FDA has both longstanding experience and expertise. Design controls allow laboratories to monitor and control the design of their tests to ensure that they are analytically and clinically valid. To obtain the full benefit of design controls, mechanisms should be implemented throughout the test lifecycle that both collect data and provide formal processes by which those data capture production and other quality problems, feed back into the design process, and inform future iterations of the test.

FDA also visited labs where separate rooms that were not part of the CLIA lab were used for the manufacture of key components, such as arrays, that are brought in to a certified CLIA lab across the hallway for use in complex high risk tests offered for clinical use. The design and manufacture of such critical components are currently without any oversight, including through CLIA, as these activities are performed outside of the CLIA certified laboratory.

Therefore, under the approach described in this paper, FDA would leverage certification to CLIA requirements, even though they are not fully consistent with FDA QS requirements, and, for LDTs made within a CLIA-certified laboratory, narrowly focus its assessment on only three FDA QS requirements that address aspects of the test development process not covered by CLIA: design controls; acceptance activities (i.e., mechanisms to ensure that products meet specified requirements coming into the laboratory and throughout testing); and procedures for implementing corrective and preventive actions (CAPA) (i.e., activities to ensure that specific quality problems, including those detected via acceptance testing, are corrected and that changes are made to prevent them from happening in the future). Laboratories may need to expand their existing CAPA activities to cover the design and development phase, and this will help them offer improved tests over time.

FDA would expand its third party inspection program for LDTs so that many of these postmarket inspections could be conducted by FDA-accredited third parties. Such third parties could include AOs and State Departments of Health who already conduct CLIA survey inspections if they meet the requirements for this FDA program. This would allow such third parties, when appropriate, to inspect for the three additional FDA QS requirements at the time of a routine CLIA survey inspection. FDA has already begun working towards this by exploring opportunities to coordinate with and leverage existing programs, such as NYSDOH's CLEP and the programs run by organizations approved by CLIA to accredit laboratories.

POSTMARKET SURVEILLANCE

Postmarket surveillance is a collection of processes and activities FDA uses to monitor the performance of tests once they are on the market to ensure tests continue to perform as intended, among other things. This type of oversight is critical in particular because laboratories and other test developers may make modifications to their tests and processes that are not reviewed by FDA or an accredited third party and that can impact the performance of their tests. These activities are designed to generate information to identify poorly performing tests and other safety problems, accurately characterize real-world performance and clinical outcomes, and facilitate the development of new tests, or new uses for existing tests.

Initially laboratories would report serious adverse events to FDA for all tests except: traditional LDTs²⁵, LDTs intended solely for public health surveillance²⁶, certain stem cell/tissue/organ transplantation LDTs²⁷, and LDTs intended solely for forensic use²⁸. In the future, we may be able to decrease or discontinue such reporting as efforts to monitor the performance of tests and other technologies and their impact on patients by leveraging data collected as a part of clinical practice ("real-world data") mature.²⁹

Recognizing that laboratories may need additional time to come into compliance with the QS regulations, even for new and significantly modified tests, these laboratories would have an additional two years beyond the premarket review phase-in to meet QS regulation requirements. Initial inspections would be educational in nature as FDA and laboratories work together to bring this additional level of quality to the design and manufacture of LDTs.

CONCLUSION

Many stakeholders, in addition to FDA, have indicated that there is a public health need for greater oversight of LDTs. For example, payers such as CMS expect FDA review of analytical and clinical validity to precede determinations of clinical utility for coverage. Extensive stakeholder feedback further confirmed the importance of balancing the unique qualities of LDTs, while still providing a reasonable assurance that such tests are analytically and clinically valid. An oversight approach should be undertaken in an efficient manner that effectively leverages, without duplicating, CLIA requirements, keeping in mind that CLIA certification only includes the laboratory where such tests are performed. It should include many of the same features that have been proposed by various groups recommending greater oversight of LDTs. Such an approach could appropriately balance patient protection with continued access and innovation. FDA looks forward to continuing to work with all stakeholders in future conversations around the right path forward on LDT oversight.

¹ <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm519540.htm>

² Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf>

³ The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies
<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf>

⁴ 21st Century Cures: Examining the Regulation of Laboratory Developed Tests, Statement of Jeffrey Shuren, M.D., J.D., Director, Center for Devices and Radiological Health, Food and Drug Administration, Department of Health and Human Services, before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives. September 9, 2014. <http://www.fda.gov/NewsEvents/Testimony/ucm415867.htm>

⁵ Examining the Regulation of Diagnostic Tests and Laboratory Operations, Statement of Jeffrey Shuren, M.D., J.D., Director, Center for Devices and Radiological Health, Food and Drug Administration, Department of Health and Human Services, before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives. November 17, 2015. <http://www.fda.gov/NewsEvents/Testimony/ucm473922.htm>

⁶ Direct-to-Consumer Genetic Testing and the Consequences to the Public, Statement of Jeffrey Shuren, M.D., J.D., Director, Center for Devices and Radiological Health, Food and Drug Administration, Department of Health and Human Services, before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives. July 22, 2010. <http://www.fda.gov/NewsEvents/Testimony/ucm219925.htm>

⁷ Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071455.pdf>

⁸ Public Meeting on Oversight of Laboratory Developed Tests, July 20, 2010
<http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM226204.pdf>

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- ⁹ National Human Genome Research Institute (1997). *Promoting Safe and Effective Genetic Testing in the United States*. <http://www.genome.gov/10001733>.
- ¹⁰ Secretary's Advisory Committee on Genetic Testing (2000). *Enhancing the Oversight of Genetic Tests: Recommendations of SACGT*. http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf
- ¹¹ Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). U.S. system of oversight of genetic testing: a response to the charge of the Secretary of Health and Human Services. Washington (DC): Department of Health & Human Services. April 2008. <http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS>
- ¹² Institute of Medicine. *Evolution of Translational Omics: Lessons Learned and the Path Forward*. Washington, DC: The National Academies Press, 2012.
- ¹³ Representative Letter to OMB Urging Release of LDT Guidance. June 2013. <https://louise.house.gov/media-center/press-releases/slaughter-calls-transparency-diagnostics-testing>
- ¹⁴ Senator Letter to OMB Urging Release of LDT Guidance. July 2014. http://www.markey.senate.gov/imo/media/doc/2014-07-02_Deese_LDTs.pdf
- ¹⁵ Cancer Leadership Council Letter to OMB Urging Release of LDT Guidances. November 2012. <http://www.cancerleadership.org/policy/fda/text/121121t.html>
- ¹⁶ Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf>
- ¹⁷ Public Workshop – Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs), January 8-9, 2015. <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm423537.htm>
- ¹⁸ College of American Pathologists' Legislative Proposal for Laboratory Developed Tests (LDT), September 14, 2015. <http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/2015-cap-ldt-legislative-proposal.pdf> and <http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/legislative-ldt-faqs.pdf>
- ¹⁹ Association for Molecular Pathology's Proposal for Modernization of CLIA Regulations for Laboratory Developed Testing Procedures (LDPs). August 14, 2015. <https://www.amp.org/advocacy/documents/AMPCLIAmodernizationproposalFINAL8.14.15.pdf>
- ²⁰ Diagnostic Test Working Group's Proposed Regulatory Framework for In Vitro Clinical Tests. March 5, 2015. http://www.fdalawblog.net/DTWG_final_proposal.pdf
- ²¹ American Clinical Laboratory Association letter to the Office of Information and Regulatory Affairs, Office of Management and Budget. November 11, 2016. <http://www.acla.com/wp-content/uploads/2016/11/2016-Nov-11-ACLA-Letter-to-OIRA-re-LDTs.pdf>
- ²² Discussion Draft on the Regulation of Diagnostic Tests and Laboratory Operations. October 22, 2015. Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives. http://docs.house.gov/meetings/IF/IF14/20151029/104127/BILLS-114pih-HR_.pdf
- ²³ 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).
- ²⁴ Thacker SB, Berkelman RL. History of public health surveillance. In: *Public Health Surveillance*, Halperin W, Baker EL (Eds.): New York; Van Nostrand Reinhold, 1992.

²⁵ Components used in a traditional LDT are required to be legally marketed and, therefore, would be under the quality system of the manufacturer. The clinical interpretation of the results is appropriately overseen by CLIA.

²⁶ Tests used solely for public health surveillance are not used to guide treatment.

²⁷ Consistent with a 2011 recommendations from the Secretary’s Advisory Committee on Organ Transplantation (ACOT) and the Advisory Council on Blood Stem Cell Transplantation (ACBSCT), 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 allele typing; or for antibody screening and monitoring; or for the purpose of conducting real and “virtual” crossmatch tests. ACOT minutes available at: <http://www.organdonor.gov/legislation/acotaugust2011notes.html>. ACOT meeting recommendations available at: <http://www.organdonor.gov/legislation/acotrecs5354.html>. ACBSCT meeting minutes available at: http://bloodcell.transplant.hrsa.gov/about/advisory_council/meetings/notes/files/acbsctsummarynotesnov2011.pdf. ACBSCT meeting recommendation available at: http://bloodcell.transplant.hrsa.gov/about/advisory_council/recommendations/rec17_21/index.html#rec17”

²⁸ Tests used solely for forensic use have different oversight mechanisms available.

²⁹ For example, FDA is working with other medical device ecosystem stakeholders to establish the National Evaluation System for health Technology (NEST) through the Medical Device Innovation Consortium. See Shuren, J, Califf RM, *Need for a National Evaluation System for Health Technology*, JAMA, 2016;316(11):1153-1154.