Anticipated Framework for Regulatory Oversight of Laboratory Developed Tests

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Historically, the U.S. Food and Drug Administration (FDA) has exercised enforcement discretion with respect to most laboratory-developed tests (LDTs) and has not required laboratories that furnish LDTs to comply with FDA's regulatory requirements for medical devices, including registration and listing, pre-market review and post-market controls. In recent years, however, FDA has publicly stated that it intends to regulate LDTs as medical devices, primarily due to concerns that the Clinical Laboratory Improvement Amendments of 1988 and its implementing regulations (CLIA) do not require pre-market review of the clinical claims associated with LDTs.

The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) requires the FDA to give two congressional committees (the House Committee on Energy and Commerce and the Senate Committee on Health, Education, Labor and Pensions) 60 days' notice of the agency's intent to issue draft or final guidance on the regulation of LDTs, as well as the anticipated contents of such guidance. Under this requirement, on July 31, 2014, the FDA sent these committees the anticipated details of two draft guidance documents—entitled "Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)" and "FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)," respectively—that outline the agency's proposed regulatory framework for LDTs. In these documents, FDA describes its priorities for enforcing pre- and post-market requirements for LDTs and how it intends to phase in enforcement of regulatory requirements for LDTs.

Note: Because neither of these documents has been published as "draft guidance," the FDA is not accepting public comments regarding either document at this time. The agency is expected, however, to publish the documents as draft guidance substantially unchanged and to announce the creation of a docket for public comment regarding the documents, effective on or after September 29, 2014.

Scope

When officially published, the documents will provide clinical laboratories instructions regarding the regulatory requirements FDA intends to extend to LDTs. Under the draft documents, FDA defines an LDT as "an [*in vitro* diagnostic (IVD) device] that is intended for clinical use and designed, manufactured, and used within a single laboratory." FDA defines a "single laboratory" as a facility with a single CLIA certificate.

According the FDA's definition, a test is not an LDT if it is designed or manufactured, completely or partly, outside of the laboratory that offers and uses the test. Consistent with this limitation, FDA states that the following tests would not be considered an LDT under the anticipated framework:

- A test developed by one laboratory in a multi-laboratory entity that is transferred to another clinical laboratory (or laboratories) within the entity's network;
- A test developed by an academic institution that is subsequently manufactured and utilized by a private corporation that owns a CLIA-certified laboratory;

- A test that incorporates a "key component (*e.g.*, coated microtiter plate, specialized specimen collection kit)" manufactured by a third party; and
- A test designed by a specification developer, but validated and used by a laboratory

Summary of Anticipated Policy

As expected, FDA indicates that it intends to end its policy of general enforcement discretion towards LDTs, and proposes the implementation of a risk-based regulatory framework. To this end, the FDA will rely on its existing medical device classification system to evaluate the risk of a category of LDTs and, informed by industry's interest in participating in the classification process, use expert advisory panels to help classify tests not previously classified by FDA. In determining the risk an LDT poses to a patient (or the user), FDA will consider several factors, including:

- Whether the test is intended for use in high-risk diseases/conditions or patient populations;
- Whether the test 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;
- Potential consequences/impact of erroneous results; and
- Number and type of adverse events associated with the test

FDA intends to issue draft guidance that describes what the agency generally considers to be a Class I, Class II or Class III device within 24 months of publishing final guidance on the LDT regulatory framework.

MAIN ELEMENTS OF FDA'S FRAMEWORK FOR REGULATORY OVERSIGHT

Continued Enforcement Discretion (In Full) for Certain Categories of LDTs

FDA does not intend to enforce its registration and listing [nor is FDA requesting notification (see below)], adverse event reporting, pre-market review or quality system requirements for:

- LDTs used solely for forensic (law enforcement) purposes
- LDTs used in CLIA-certified, high-complexity histocompatibility laboratories for tests used in connection with organ, stem cell and tissue transplantation to perform high-resolution allele typing, tests used in antibody screening and monitoring, and cross-match tests (real and virtual). This exception does not apply to tests used in blood banking.

Notification to FDA of LDTs Manufactured by a Laboratory (or Compliance with the Agency's Registration and Listing Requirements)

FDA intends to continue to exercise enforcement discretion with respect to registration and listing requirements for laboratories that manufacture LDTs, provided such laboratories notify FDA that they are manufacturing LDTs and provide basic information regarding each LDT. The required timing of such notification depends on the relationship between the date of the test's initial commercial availability and the date of publication of the final guidance.

For LDTs that are commercially available when the final guidance document is published or LDTs that enter the market within six months of the final guidance being published, laboratories should provide notification information to the FDA within six months of the date the final guidance is published.

For LDTs that are first commercialized at least six months after the final guidance is published, laboratories should notify the FDA prior to offering the test for clinical use.

Information should be submitted online through the FDA website. Notification is expected to occur once for each LDT, although additional notification should be provided if significant changes are made.

Note: Presumably, the rationale for FDA's offering a notification option rather than requiring registration and listing is to avoid the near-term imposition of medical device tax liability, which is triggered by registration and listing. Under this framework, a laboratory is not required to register and list until a pre-market submission is made.

Laboratories that do not notify the agency that they are manufacturing LDTs will be required to comply with the registration and listing requirements for devices. FDA does not intend to enforce these requirements with respect to LDTs, however, until a pre-market submission [*i.e.,* pre-market approval (PMA) or 510(k)] has been made to the agency.

MDR Requirements

Beginning six months following publication of the final guidance, FDA intends to cease its exercise of enforcement discretion with respect to medical device reporting (MDR) reporting requirements for laboratories that offer LDTs. The mechanics of the MDR process are outlined in the above-referenced anticipated draft guidance.

Pre-Market Review Requirements

FDA intends to phase in the enforcement of pre-market requirements for certain LDTs based on the risk associated with the test. The agency intends to focus its initial efforts on the highest risk tests and gradually phase in enforcement for lower risk tests over time.

CONTINUED ENFORCEMENT DISCRETION

FDA intends to continue enforcement discretion with respect to pre-market review requirements for the following types of LDTs:

- Low-risk LDTs (Class I devices)
- LDTs for rare diseases (*i.e.*, tests for which the number of persons who may be tested is fewer than 4,000 per year)
- Traditional LDTs—tests like those available when FDA began its policy of generally exercising enforcement discretion over LDTs in 1976. In considering whether a test is a traditional LDT, FDA intends to consider the following:
  - Whether the test meets the definition of an LDT (as defined in the guidance);
  - Whether the test is manufactured and used by a health care facility laboratory for a patient that is being diagnosed and/or treated at that same facility (or within the facility's system);
  - Whether the test is comprised of only legally marketed components and instruments (*e.g.*, analyte-specific reagents, general purpose reagents); and
  - Whether the test is interpreted by qualified laboratory professionals, without the use of automated instrumentation or software for interpretation

This definition provides a fairly narrow exemption. LDTs that include components other than analyte-specific reagents and general purpose reagents, such as research-use only reagents, presumably would not fit under this definition. This exemption would not be available to laboratories outside health care facilities.

- LDTs for unmet needs—tests that serve unmet needs until a comparable FDA-cleared or -approved device becomes available; in considering whether a test meets unmet needs, FDA intends to consider the following:
  - Whether the test meets the definition of an LDT (as defined in the guidance);
  - Whether there is no FDA-cleared or -approved test available for that specific intended use; and
  - Whether the test is manufactured and used by a health care facility laboratory for a patient that is being diagnosed and/or treated at that same facility (or within the facility's system)

Key to understanding the scope of this exemption will be FDA's intention regarding "specific intended use." Note that the term "intended use" for medical devices refers to a distinct concept from "indication for use." This exemption is also not available for laboratories outside healthcare facilities.

END OF ENFORCEMENT DISCRETION FOR CERTAIN HIGH-PRIORITY LDTs

The agency intends to begin enforcing pre-market review requirements beginning 12 months after the guidance is finalized for the following types of LDTs:

- LDTs with the same intended use as a cleared or approved companion diagnostic
- LDTs with the same intended use as an FDA-approved Class III medical device

- Certain LDTs for determining the safety or efficacy of blood products

For currently marketed tests in the above categories, FDA intends to exercise enforcement discretion with respect to pre-market review requirements for 12 months following publication of the final guidance. If a laboratory makes an appropriate pre-market submission during this 12-month period, FDA intends to continue exercising enforcement discretion while the submission is under FDA review.

For new LDTs (*i.e.*, an LDT that becomes available after publication of the final guidance) in the above categories, FDA intends to begin enforcing pre-market review requirements immediately upon publication of the final guidance.

PHASED-IN ENFORCEMENT OF PRE-MARKET REQUIREMENTS FOR OTHER LDT CATEGORIES

For LDTs other than those listed above, FDA plans to use advisory panels to prioritize tests on the basis of risk.

For the remaining Class III LDTs, FDA expects to announce its priority list within 24 months of publishing the final guidance. In the priority list, FDA will describe the order in which the agency will enforce pre-market requirements and when the agency intends to enforce the requirements for each category of tests.

The agency intends to start enforcing the requirements for the highest-priority remaining Class III LDTs beginning no less than 12 months after the priority list is announced. LDTs likely to be included in this highest priority group include:

- Devices that act like companion diagnostics
- Screening devices for serious diseases and/or conditions intended for use in asymptomatic patients with no other available confirmatory diagnostic product or procedure
- Diagnostic devices for certain infectious diseases with high-risk intended uses

If a pre-market submission (*e.g.*, PMA or Investigational Device Exemption) 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 requirements for LDTs in a particular category, however, FDA will expect laboratories that develop new LDTs in these categories to comply with pre-market review requirements before marketing of such LDTs.

FDA intends to finish phasing in the enforcement of requirements for Class III devices within five years of issuing final guidance. FDA intends to phase-in enforcement of pre-market requirements for Class II devices after it has finished the Class III phase-in process. FDA expects to announce the enforcement prioritization of Class II devices within four years of finalization of the guidance and complete phased-in enforcement of the pre-market requirements for Class II devices within nine years of finalizing the guidance.

EVALUATION OF CLINICAL VALIDITY

FDA expects that for many LDTs, clinical validity has already been established in literature. If appropriate, FDA intends to leverage information from the existing clinical literature that establishes clinical validity in lieu of requiring additional studies. In these cases FDA may still require studies demonstrating device performance (*e.g.*, analytical evaluations).

A critical issue is whether FDA will allow treatment selection claims based upon clinical literature. For a diagnostic test to be eligible for coverage under Medicare (and most private plans, as well), the test must be used by the treating physician in the management of the patient so that treatment selection claims are highly relevant for successful commercialization of diagnostic tests. Historically, FDA has been reluctant to allow treatment selection claims without evidence from prospective clinical trials. Moreover, if FDA does accept evidence from the literature to support pre-market clearance or approval of LDTs, will the agency also accept these types of data for currently regulated IVD test kits?

THIRD-PARTY REVIEW

While FDA will generally review pre-market approvals for high-risk (Class III) LDTs, the agency believes that it will often be appropriate for third parties to review 510(k) submissions for lower risk (Class II) LDTs.

QSRs

FDA intends to exercise enforcement discretion with respect to quality systems requirements (QSR) until the manufacturer of an LDT submits a PMA or FDA issues a 510(k) clearance

order. The clinical laboratory that manufactures and uses the LDT will be responsible for having a quality system in place that meets regulatory requirements either at the time of the PMA submission or prior to market launch for cleared devices. The agency also specifically encourages laboratories to implement design controls when developing new LDTs.

Implications

The documents announce an important change in the regulatory requirements for LDTs. In general, these long-anticipated documents are consistent with the approach to regulation of LDTs that FDA described in presentations during a public meeting the agency held in July 2010.

In these documents, the agency addresses some concerns that stakeholders have raised with FDA during the past four years, including the agency's creation of a "notification" procedure, which would allow laboratories to comply with regulatory requirements without triggering the medical device tax, the agency's intent to continue its enforcement discretion with respect to currently available tests while the agency reviews pre-market submissions for such tests, and the agency's intent to exercise enforcement discretion with respect to the pre-market requirements for tests for whom the eligible population is extremely small.

At the same time, a number of key questions regarding FDA's regulation of clinical laboratories as medical device manufacturers and regulation of LDTs as medical devices remain open.

DEFINITION OF LDT IS NARROW: MANY LDTs OFFERED TODAY WOULD NOT FIT

The anticipated draft guidance considers a test an LDT only insofar as it is designed, manufactured and used within a single clinical laboratory with a single CLIA certificate. With certain limited exceptions, CLIA requires each laboratory facility to have its own certificate. A laboratory that operates in multiple buildings that are not directly connected (*e.g.*, two buildings across the street from one another) may have multiple CLIA certificates even though it is a single laboratory owned and operated by a single entity. Such laboratory would not meet the definition of an LDT under the anticipated draft guidance.

Under the anticipated draft guidance, a test that involves a key component manufactured by a third party would not be considered an LDT. It is not clear how broad or narrow FDA intends the scope of this limitation to be. Any number of components involved in the performance of an LDT could be considered a key component. If that term is interpreted broadly by FDA, the number of tests meeting FDA's definition of LDT may be very limited.

In the anticipated draft guidance, FDA recognizes that some tests offered by laboratories as LDTs would not meet the agency's definition of LDT. FDA indicates that such tests are "out of compliance with the FD&C Act". However, the FDA also announces "[I]n 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 [this guidance], to any IVD that is offered as an LDT by a CLIA-certified laboratory."

APPLICATION OF REGULATIONS MAY RESTRICT LABORATORIES' FLEXIBILITY TO MAKE TIMELY, INCREMENTAL CHANGES TO INCORPORATE NEW SCIENTIFIC DISCOVERIES

Currently, under CLIA regulations, a laboratory that makes an improvement to an established LDT may begin to perform the revised test once it has established performance specifications and other quality controls and documented the changes reflected in the revised test. Under the anticipated draft guidance, a laboratory that modifies an FDA-approved or -cleared test may be subject to certain time-consuming pre-market requirements, such as submission of a subsequent 510(k) notice or a supplemental PMA.

Implementation of medical device regulations over laboratories and the entire test system of an LDT would result in substantially different requirements than laboratories offering LDTs currently operate under, with respect to FDA-cleared or -approved IVDs. With an FDA-cleared or approved IVD, a laboratory currently is free to adopt process changes (*e.g.*, application of automated specimen preparation for an IVD for which labeling describes only a manual preparation), as long as the laboratory has validated the process change under CLIA requirements. If an LDT is considered to be a finished medical device, a process change to the operation of the test would require consideration of the need for a supplemental FDA submission and delay in implementation of the change until clearance or approval of the change.

DOCUMENTS DO NOT PROVIDE GUIDANCE ON THE AMOUNT OR TYPE OF CLINICAL VALIDITY DATA REQUIRED TO SUPPORT APPROVAL OR CLEARANCE

The agency acknowledges that existing publications may be sufficient to establish the clinical validity of certain LDTs. The documents do not, however, provide any guidance regarding the characteristics of studies (*e.g.*, design, sample size, statistical analysis plan) that the agency will look to support such a determination.

This has been an area of particular concern to laboratories developing advanced or molecular LDTs in which multiple markers and extensive bioinformatics are involved in producing a patient-specific result that is intended to inform patient management decisions.

Insofar as LDTs may be cleared or approved with labeling restricting use for treatment selection (as is the case with a number of LDTs that have been cleared by FDA), actual use of such tests for treatment selection would be "off-label." Although off-label use in the practice of medicine is accepted by FDA for medical devices, such as IVDs used off-label by CLIA-certified laboratories, it is unclear what risks such use would raise for clinical laboratories once they are considered to be medical device manufacturers as well as licensed and certified clinical service providers.

DOCUMENTS DO NOT ADDRESS SEVERAL PRACTICAL ISSUES PERTAINING TO REGULATION OF LDTs AS MEDICAL DEVICES

Unlike an IVD test kit, an LDT is a not a physical item that can be transferred in commerce; rather, it is a service performed by a clinical laboratory. As such, stakeholders have raised a number of questions to FDA, including: What is the regulated device within the laboratory test operation? To whom is the labeling addressed—the laboratory or the treating physician?

DOCUMENTS DO NOT ADDRESS CERTAIN INCONSISTENCIES AND CHALLENGES BETWEEN FDA AND CLIA OVERSIGHT FRAMEWORKS

For example, CLIA's requirement for the dissemination of information regarding the use of laboratory tests by CLIA-mandated clinical consultations can conflict with FDA's limitations on promotional communications by device manufacturers. Moreover, certain provisions of the FDA's QSRs, such as design controls, raise significant challenges for laboratories operating under CLIA quality system regulations.

FDA RESOURCES REQUIRED TO REGULATE LDTs

LDTs are performed in thousands of laboratories across the country; a single laboratory may perform many LDTs. Although the agency proposes to continue enforcement discretion with respect to the pre-market requirements for certain LDTs, many tests will be subject to pre-market requirements under the terms of the (anticipated) proposed guidance. The agency will need substantial additional resources to implement regulatory oversight of these services.

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