

FDA Issues Discussion Paper on Possible Regulatory Approach for Laboratory Developed Tests

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Medical Devices and Diagnostics

On January 13, 2017, the U.S. Food and Drug Administration (FDA or Agency) released a [discussion paper](#) synthesizing public feedback on FDA's 2014 draft guidance documents and outlining a possible approach to regulation of laboratory developed tests (LDTs) (Discussion Paper). This approach is intended to "advance the public discussion by providing a possible approach to spur further dialogue" and "to respond to stakeholder feedback and attempt to balance patient protection with continued access and innovation."

This Discussion Paper has no legal status, is not enforceable, and does not address the fundamental legal question regarding FDA's assertion of jurisdiction over LDTs. In addition, the discussion paper "does not represent a final version of the LDT draft guidance documents that were published in 2014."

As we previously [reported](#), FDA announced on November 18, 2016, that it would not finalize the draft guidance entitled [Framework for Regulatory Oversight of Laboratory Developed Tests](#) (Draft Guidance) prior to end of the Obama Administration.

FDA claims that there is "a growing consensus that additional oversight of LDTs is necessary, as reflected in several recent oversight proposals put forward by some organizations", and asserts that these proposals "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."

We highlight below key components of the Discussion Paper's suggested approach for prospective oversight of LDTs, some of which significantly diverge from the approach outlined in FDA's Draft Guidance.

Focused Oversight

- FDA oversight would focus on “new and significantly modified high and moderate risk LDTs...”
- FDA would not expect “previously marketed LDTs” to comply with most or all FDA regulatory requirements -- including premarket review, Quality Systems Regulation (QSR), and registration and listing. Previously marketed LDTs would be defined as those that were marketed prior to the effective date of the new oversight model, and would be referred to as “grandfathered LDTs.” However, there would be two potential exceptions to this grandfathering: (1) when FDA considers regulation to be “necessary to protect the public health” and (2) when an LDT has been “significantly modified.”
- Certain categories of “new and significantly modified LDTs” would not be expected to meet premarket review, QSR, and registration and listing requirements, unless “necessary to protect the public health.” These categories include: (1) low risk LDTs; (2) LDTs for rare diseases; (3) traditional LDTs; (4) LDTs intended solely for public health surveillance; (5) certain LDTs for transplantation when performed in CLIA-certified, high-complexity histocompatibility laboratories; and (6) LDTs intended solely for forensic use.
 - “Traditional LDTs” are defined by FDA as “tests that use components that are legally marketed for clinical use 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” are those tests “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 control.”
- In the Discussion Paper, the Agency proposes a definition of “LDTs for unmet needs” that is broader than the definition proposed in the Draft Guidance. Whereas the Draft Guidance limited these LDTs to those performed by a healthcare system laboratory, the Discussion Paper includes “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.” FDA proposes permitting laboratories to have up to 90 days after offering an LDT for an unmet need to submit a premarket submission demonstrating the the LDT is analytically and clinically valid.
- FDA would reserve the right to enforce premarket review, QSR, and other application requirements for *any* LDT if: (1) the LDT “is not analytically or clinically valid or there is an absence of sufficient data to support its analytical or clinical validity”; (2) the entity offering an LDT has engaged in deceptive promotion; or (3) “there is a reasonable probability that the LDT will cause death or serious adverse health consequences.”

Risk-Based, Phased-In Oversight

- In the Draft Guidance, FDA recommended a nine-year, phased-in timeline. In contrast, the Discussion Paper proposes a four-year timeline, which FDA believes is appropriate given the approach’s proposed “grandfathering” of LDTs currently on the market. The Discussion Paper states as follows:

- 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.
- Tests introduced between the effective date of the framework and the phase-in date could continue to be offered for clinical use during the period of premarket review.
 - Registration and listing would occur at the time an LDT receives marketing authorization.

Evidence Standards

- FDA asserts that it should be the Agency to conduct premarket review of analytical and clinical validity, not CMS. FDA further states that its premarket review would be complementary, not duplicative of, CMS's postmarket oversight.
- According to FDA: "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."
- Since CMS requires laboratories to establish a test's performance characteristics, FDA expects that laboratories would not have to collect additional data to demonstrate analytical validity in a submission for FDA clearance or approval.
- FDA recognizes that clinical validity "can often be supported by literature, well-curated databases, or other appropriate sources that meet the valid scientific evidence standard", particularly if the LDT is an established test. Once clinical validity for a certain test 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."

Third-Party Review

- The Agency would increase its third-party premarket review program to include eligible LDTs and is already researching opportunities to leverage existing programs, like New York State's Clinical Laboratory Evaluation Program and programs run by accreditation organizations (AOs) approved by CMS to conduct CLIA accreditation inspections.
- FDA notes that it is "exploring accepting [the New York State Department of Health's premarket] review in lieu of its own."

Clinical Collaboratives

- Under the regulatory framework envisioned by FDA, the Agency would increase its collaborative work with the health care professional, laboratory, and conventional IVD manufacturer communities to: (1) develop measurement and review standards for analytical validity for tests “where feasible and beneficial”; (2) gather evidence to demonstrate clinical validity for specific types of tests; and (3) develop FDA-recognized standards for use in determining clinical validity for specific types of tests.
- By applying these recognized standards for analytical and clinical validity, FDA and accredited third-party reviewers could rely in part or wholly the interpretations made by such clinical collaboratives.

Transparency

- FDA’s Discussion Paper states that evidence of analytical and clinical validity of *all* LDTs would be made publicly available -- through publication in a journal, on the laboratory’s website, or elsewhere. FDA views this transparency as necessary “since understanding the test performance and how it was derived is crucial to understanding how to use the results.”
- The Agency would publish its review memorandum for FDA-reviewed tests. For tests not reviewed by FDA, the Agency would encourage laboratories to make validity information public and work with the clinical community on the content and format for providing such information.
- FDA recognizes that laboratories should be able to respond to specific requests from healthcare professionals “to run a particular test that is not FDA reviewed for the requested intended use” but only “for the sole purpose of diagnosing or treating a specific individual.”

Modifications

- To try to make FDA regulation of test modifications less burdensome, the Agency would permit and encourage laboratories to submit “prospective change protocols” in premarket submissions. These change protocols would outline: (1) specific types of anticipated changes, (2) processes that will be followed to implement them, and (3) the criteria that will be satisfied prior to implementation.
- After receiving marketing authorization for an LDT, a laboratory could make a modification in accordance with the change protocol without a new submission to FDA.
- Premarket review of modifications to an already-marketed test would apply to both changes to a “grandfathered” LDT and modification of an IVD kit, but could 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.”

Quality System Requirements

- Under its oversight proposal, FDA claims that it “would leverage certification to CLIA requirements, even though they are not fully consistent with FDA QS requirements.” FDA states that its focus would be on compliance with only three QSR requirements that

address features of the test development process not covered by CLIA: (1) design controls, (2) acceptance activities, and (3) procedures for implementing corrective and preventive actions (CAPAs).

- The Agency would expand its third-party inspection program for LDTs to enable FDA-accredited third parties to conduct postmarket inspections. Third parties might include AOs and State Departments of Health, which could inspect for the three additional QSR requirements at the time of a routine CLIA survey inspection.

Postmarket Surveillance

- Under the proposed framework, laboratories would be required to report serious adverse events to FDA for all tests except traditional LDTs, public health surveillance LDTs, stem cell/tissue/organ transplantation LDTs, and forensic use LDTs.
- The Agency recognizes that it may 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.”
- Laboratories would have an additional two years after premarket review phase-in to meet the applicable QSR requirements.

FDA’s Discussion Paper outlines the current preferred regulatory approach of the FDA (during the final days of the Obama Administration), as Congress and stakeholders focus on possible future legislative efforts. We will continue to monitor legislative and regulatory developments relating to LDTs.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our Medical Devices and Diagnostics practice:

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