

FDA to Strengthen Oversight of Certain In Vitro Diagnostic Devices

In the wake of a new Medicare reimbursement framework, FDA plans stricter regulation of some in vitro diagnostic devices.

On July 31, 2014, the U.S. Food and Drug Administration (FDA; Agency) announced its intent to strengthen regulation of certain in vitro diagnostics (IVDs), including laboratory developed tests (LDTs). On the same day, the Agency also released final guidance on IVD companion diagnostic devices. These actions follow the enactment of substantial legislative changes to Medicare reimbursement methodologies for certain LDTs and other tests performed in laboratories certified under the Clinical Laboratory Improvement Amendments (CLIA). The Centers for Medicare & Medicaid Services (CMS) has solicited stakeholder views and concerns about the implementation of the legislation, including the promulgation of regulations to be published in 2015.

FDA first released a notice of its intent to issue two new draft guidance documents related to the regulation of LDTs on or after September 29, 2014. FDA has historically exercised its enforcement discretion to exclude LDTs from the regulatory requirements applicable to other medical devices. If the draft guidance documents are finalized, LDTs will, for the first time, be subject to FDA's comprehensive medical device regulations. The process is anticipated to be phased in over nearly a decade, and will utilize a risk-based framework. In an Agency statement, FDA Commissioner Margaret A. Hamburg, M.D. said, "[the] action demonstrates the agency's commitment to personalized medicine, which depends on accurate and reliable tests to get the right treatment to the right patient."¹

FDA also released its final guidance on IVD companion diagnostic devices, which largely implements the Agency's draft guidance, originally issued in July 2011. The final guidance provides that FDA generally will not approve any therapeutic product that requires an IVD companion diagnostic device for its safe and effective use before the IVD companion diagnostic device is approved or cleared for that indication. Compliance with this guidance will require coordination between FDA's Center for Devices and Radiological Health (CDRH) and its Centers for Drug Evaluation and Research (CDER) and Biologics Evaluation and Research (CBER).

FDA to begin enforcing regulatory requirements for LDTs

On July 31, 2014 FDA announced it intends to begin regulating LDTs, releasing a notice to the U.S. Senate Committee on Health Education, Labor and Pensions, and the U.S. House of Representatives Committee on Energy and Commerce. The notice declares that FDA intends to issue two draft guidance documents on the regulation of LDTs (together, Draft Guidances).² Under the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA), FDA is required to provide notice to both Committees at least 60 days before issuing any draft or final guidance on the regulation of LDTs under the Federal

Food, Drug, and Cosmetic Act (FDCA).³ Consistent with that requirement, FDA's notice indicates that the Agency will not publish the draft guidance documents identified in the notification or establish a docket until at least 60 days after the notification, or September 29, 2014. Both proposed draft guidance documents were released in full along with the notice.

The first draft guidance, entitled *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* (Draft Framework Guidance), sets out the proposed enforcement framework for LDTs. The second, entitled *FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)* (Draft Notification Guidance), details the proposed FDA notification and medical device reporting requirements.

The Draft Framework Guidance proposes a framework that reflects a risk-based approach toward FDA oversight, both in terms of the ultimate level of oversight and the implementation timeline.

Products covered by the draft guidance documents

While the guidances adopt a narrow definition of LDTs, the phased-in approach to enforcement laid out in the Draft Framework Guidance will extend broadly to any IVD offered as an LDT by a CLIA-certified laboratory, regardless of whether the IVD meets the limited definition.

FDA defines the term "laboratory developed test" as an IVD intended for clinical use and designed, manufactured and used within a single laboratory." Under this narrow definition, any diagnostic tests that are designed or manufactured, even partly, outside the laboratory that offers and uses them are not considered LDTs. This limited definition implies that FDA does not consider its current exercise of enforcement discretion to apply to many of the tests that have been widely characterized as LDTs. Thus, FDA appears to adopt the position that such tests, including, for example, any test developed in one clinical laboratory and then transferred to other clinical laboratories owned by the same entity, any test containing a key component that was produced by a third party contract manufacturer, and any test designed by a contract specification developer — even if the design is transferred to the clinical laboratory for final validation prior to manufacture and use — fall outside of its exercise of enforcement discretion and are currently subject to the medical device regulatory requirements.

Nonetheless, the Draft Framework Guidance explains that, "in the interest of ensuring continuity in the testing market and avoiding disruption of access to these tests," FDA intends to apply the same framework to "any IVD that is offered as an LDT by a CLIA-certified laboratory."

Proposed level of oversight

FDA intends to rely on the existing medical device classification system, which divides medical devices into three classes from the lowest risk (Class I) to the highest risk (Class III). Previously unclassified LDTs will be classified based on an assessment of risk, using expert advisory panels as appropriate. FDA intends to determine risk based on factors such as:

- 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 or pathologist would have other information about the patient to assist in making a clinical decision
- Alternative diagnostic and treatment options available to the patient
- The potential consequences or impact of erroneous results
- The number and type of adverse events associated with the test

Those tests that FDA determines pose the greatest risk will ultimately be regulated more stringently.

The Draft Framework Guidance indicates that, within 18 to 24 months after finalizing, FDA will issue a separate draft guidance document to describe the types of devices the agency considers generally to fall into each class. FDA also recognizes that some LDTs with new intended uses may automatically be classified in the highest risk class as a matter of law, but, where warranted, FDA plans to down classify such LDTs either on its own initiative or using the *de novo* process, with input from advisory panels.

Risk-based requirements

At the low end of the risk continuum, FDA will continue to exercise its enforcement discretion to exclude from medical device regulation certain low-risk LDTs. These tests include:

- LDTs used solely for law enforcement purposes
- Certain LDTs for transplantation when used in CLIA-certified, high complexity histocompatibility laboratories

FDA will not subject certain other LDTs to enforcement for compliance with pre-market review and quality systems requirements. These tests, however, eventually must comply with all other applicable regulatory requirements (except certain reporting requirements as described below). These tests include:

- LDTs that are Class I devices
- LDTs for rare diseases
- “Traditional LDTs” that reflect the types of LDTs that were available when FDA first implemented its policy of enforcement discretion in 1976
- LTDs for unmet needs, when no FDA-approved or cleared equivalent device is available

All other LDTs eventually must comply with all pre- and post-market regulatory requirements applicable to medical devices (except certain reporting requirements as described below).

Other enforcement policies

The Draft Framework Guidance provides that, even if premarket submissions are required, FDA will, if possible, permit the use of clinical literature to support a demonstration of clinical validity in lieu of clinical trials. However, FDA may still require studies demonstrating device performance. FDA will work with the laboratory community, the healthcare professional community and other stakeholders to determine whether an LDT’s clinical validity has already been established in the literature.

In addition, FDA intends to expand its third-party review program to include pre-market review of moderate risk (Class II) LDTs “as appropriate.” Under this model, FDA generally would review high-risk (Class III) LDTs requiring submission of a premarket approval application, while accrediting third-parties to carry out review of most Class II LDTs requiring premarket notification pursuant to section 510(k) of the FDCA.

Registration and listing requirements

The Draft Guidances provide an alternative to the registration and listing requirements under 21 C.F.R. Part 807 for certain owners and operators of laboratories that manufacture, prepare, propagate, compound, assemble or process LDTs. To qualify, the owner/operator must not undertake these activities with respect to any medical devices other than LDTs. Also the owner operator must timely submit notification to FDA that it is manufacturing LDTs and provide particular descriptive information regarding each of its LDTs. The required information is detailed in FDA’s proposed Draft Notification Guidance. The registration and listing requirement will apply after a premarket submission has been filed with FDA.

For all LDTs on the market within six months after the final guidance document is published, the owner/operator must submit the notification within six months of publication of the final guidance. For all other LDTs, the owner/operator must submit the notification prior to offering the LDTs for clinical use. Owner/operators must also submit notifications for all significant changes to the marketed intended use of an LDT for which a previous notification has been submitted.

Under the proposed policy, FDA will make notification data publicly available, after removing any information for which public disclosure is prohibited.

Medical device reporting (MDR) requirements

The Draft Guidances indicate that FDA intends to enforce the MDR requirements under 21 C.F.R. Part 803, Subpart E for all laboratories that manufacture LDTs, except for the categories of devices that will continue to enjoy complete enforcement discretion, described above. Enforcement will begin six months after the Draft Framework Guidance is finalized. Information about how the MDR requirements will apply to laboratories is detailed in FDA's Draft Notification Guidance.

Proposed timeline

Most of the proposed deadlines in the Draft Framework Guidance reference the date that the Draft Framework Guidance is finalized. Such finalization will likely take some time. First, the draft guidance will be issued officially for public comment and a public docket will be established no earlier than September 29, 2014. The final guidance will be published only after FDA has collected and considered any comments submitted. In addition, litigation challenging the guidance possibly could delay implementation of the proposed policy. Indeed, some industry groups have already expressed opposition to any increased regulation of LDTs.⁴

After the Draft Framework Guidance is finalized, pre-market requirements will be phased in over a nine-year period based on risk. Devices that are already in use at the time FDA initiates enforcement of the premarket review requirements will be permitted to remain in use — pending FDA's review and consideration of the premarket submission — so long as a premarket submission is timely made. Any new device that is not in use when such enforcement begins will be required to obtain premarket clearance or approval before initiating clinical use.

The first stage of enforcement will begin 12 months after the guidance is finalized for the "highest risk" LDTs, which include:

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

FDA also considers the following types of devices to be of higher concern to the agency, and therefore to be included in the earlier stages of enforcement:

- (a) Devices that act like companion diagnostics
- (b) Screening devices for serious diseases and/or conditions intended for use in asymptomatic patients with no other available confirmatory diagnostic product or procedure, such as screening devices for malignant cancers

(c) Diagnostic devices for certain infectious diseases with high-risk intended uses (e.g. devices intended to monitor cytomegalovirus and/or Epstein-Barr virus in infected, immunocompromised, or transplant patients)

FDA's enforcement timeline is summarized in the following chart.

Event	Effective date
Application of notification and significant adverse event reporting requirements	Six months after guidance is finalized
Application of premarket review requirements to the highest-risk LDTs (subset of Class III medical devices) [Note: FDA will exercise enforcement discretion to permit the continuing marketing of those highest-risk LDTs that are in use prior to publication of the final guidance, and for which a premarket submission is made within 12 months after publication pending review of the submission.]	Beginning one year after guidance is finalized
Announcement of priority list for remaining Class III LDTs	No more than two years after guidance is finalized
Application of premarket review requirements for products on priority list [Note: FDA will exercise enforcement discretion to permit the continued marketing of those high-risk LDTs that are in use prior to the time that FDA begins enforcing the premarket review requirements for that category of LDT products pending review of the submission.]	Beginning no less than three years and ending no more than five years after guidance is finalized
Announcement of priority list for moderate-risk LDTs	No more than four years after guidance is finalized
Application of premarket review requirements for moderate risk (Class II) LDTs [Note: FDA will exercise enforcement discretion to permit the continued marketing of those moderate-risk LDTs that are in use prior to the time that FDA begins enforcing the premarket review requirements for that category of LDT products pending review of the submission.]	Beginning five years and ending no more than nine years after guidance is finalized
Application of quality control requirements under 21 C.F.R. Part 820	At time of PMA submission or 510(k) clearance order

FDA issues final guidance for IVD companion diagnostic devices

On the same day that FDA published the LDT notice, FDA also released its final guidance on IVD companion diagnostic devices (Companion Diagnostic Guidance).⁵ This guidance finalizes the draft version released in July 2011. While the final guidance does not differ in any material respects from the draft guidance, it does provide some additional clarification, in response to public comments.

Like the draft version, the Companion Diagnostic Guidance applies only to “IVD companion diagnostic devices,” defined narrowly as in vitro diagnostic devices that provide “information *that is essential* for the safe and effective use of a corresponding therapeutic product.”⁶ The Companion Diagnostic Guidance does not apply to in vitro diagnostic tests that are not essential to the safe and effective use of a therapeutic product — such as assays like serum creatinine or transaminases used to monitor organ function, but not essential for the safe and effective use of a therapeutic product.

The Companion Diagnostic Guidance asserts that, when results from a diagnostic device are essential in patient treatment, health care professionals must be able to rely on those results and “inadequate performance of an IVD companion diagnostic device could have severe therapeutic consequences.”⁷ Accordingly, under the final guidance, CDRH will assess the safety and effectiveness of the IVD companion diagnostic device as used with the therapeutic product through premarket review and clearance or approval. CDER or CBER, as applicable, generally will not approve the therapeutic product before the IVD companion diagnostic device is approved or cleared for that indication. FDA therefore recommends that a therapeutic product and its corresponding IVD companion diagnostic device be developed contemporaneously, with the clinical performance and clinical significance of the IVD companion diagnostic device established using data from the clinical development program of the corresponding therapeutic product.

Like the draft version, the Companion Diagnostic Guidance provides two scenarios in which FDA may approve a therapeutic product even though an IVD companion diagnostic device is not approved or cleared contemporaneously. These include: (1) new therapeutic products for the treatment of serious of life-threatening conditions; and (2) previously approved therapeutic products that require a labelling revision to address a serious safety issue when “the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device.”⁸

FDA expects that the therapeutic product sponsor will address the need for an approved or cleared IVD companion diagnostic device in its therapeutic product development plan and recommends that sponsors consult early with FDA on the likely regulatory pathway for the IVD companion diagnostic device. For therapeutic product and companion diagnostic device applications submitted concurrently, FDA intends to issue approvals or approval and clearance for both products at the same time.⁹

The Companion Diagnostic Guidance also includes information about the required labelling for therapeutic products with IVD companion diagnostic devices, and for the companion diagnostic device. Of particular note, the guidance specifies that the therapeutic product labelling ordinarily will include information about the use of an IVD companion diagnostic device that meets the regulatory definition, and should not specify a particular manufacturer’s device.¹⁰ The final guidance also includes information about investigational use of companion diagnostic devices.¹¹

The approval of a therapeutic product and companion diagnostic device requires coordination between CDER/CBER and CDRH. The Companion Diagnostic Guidance asserts that FDA is also “developing appropriate internal policies and procedures to ensure effective communication among the relevant

centers and to promote consistent advice, efficient development of IVD companion diagnostic devices and therapeutic products, and coordinated product reviews for these devices and therapeutic products.”¹²

Recent legislative changes affecting Medicare reimbursement to CLIA-certified laboratories for diagnostic laboratory tests

FDA’s IVD regulatory changes come just after Congress enacted legislation that will significantly alter the framework for reimbursement for certain diagnostic laboratory tests performed by clinical laboratories. Section 216 of the Protecting Access to Medicare Act of 2014,¹³ which President Obama signed into law on April 1, 2014, establishes a new market-rate payment system (effective January 1, 2017), imposes new reporting requirements on laboratories (beginning January 1, 2016) and requires establishment of new reimbursement codes.

Effective January 1, 2017, CMS will determine payments under the Clinical Laboratory Fee Schedule (CLFS) using weighted-median private payor rates, *i.e.* “market rates.” The market-based payment system would replace established payment policies and final, yet-to-be-implemented policies to better reflect the actual cost of resources used in providing laboratory tests. To enable CMS to establish market rates, Section 216 requires applicable laboratories to report payment rates and volume information for each laboratory test every three years, beginning January 1, 2016. Applicable laboratories are those with a majority of Medicare revenues from Medicare’s CLFS or Medicare Physician Fee Schedule, with the possible exception of certain low-volume laboratories. For tests that qualify as “advanced diagnostic laboratory tests,” qualified laboratories will be required to report annually. An advanced diagnostic laboratory test is a test offered and furnished only by a single laboratory and not sold for use by a laboratory other than the original developing laboratory, and one of the following:

- (a) Is an analysis of multiple biomarkers of DNA, RNA, or proteins combined with a unique algorithm to yield a single patient-specific result
- (b) Is cleared or approved by FDA
- (c) Meets other similar criteria established by the U.S. Department of Health and Human Services

CMS is required to establish data collection regulations no later than June 30, 2015.

CMS will use the reported data to establish “market rates” for each applicable test. Payment for each test will be weighted by volume for each payor and each laboratory. Payment rates will no longer be subject to adjustments, such as budget neutrality or annual updates. Although market-rate payments will begin January 1, 2017, payment reductions will be phased-in through 2022. For payments between 2017 and 2019, the annual reduction is capped at 10 percent and then at 15 percent through 2022. For an initial period, new diagnostic laboratory tests will be paid using cross-walking or gap-filling methodology. For new advanced diagnostic laboratory tests, the payment rate for the first nine months will be the “actual list charge,” or publicly available rate, on the first day the test is available for purchase by a private payor. The payment rate is subject to post-payment recoupment, however, if it is later found to be greater than 130 percent of the market rate. Payment amount decisions are not appealable, and this payment rate will not apply to hospital tests included in a bundled payment.

In addition, CMS must establish temporary Healthcare Common Procedure Coding System (HCPCS) codes for new advanced diagnostic laboratory tests and new laboratory tests cleared or approved by FDA. For any existing tests that are paid by Medicare but do not currently have unique codes, CMS must establish new unique codes by January 1, 2016.

The legislation requires CMS to consult with an outside expert advisory panel on establishing payment rates and coverage, as well as payment decisions for new clinical laboratory tests beginning July 1, 2015. The legislation also authorizes CMS to designate up to four contractors to establish laboratory coverage policies or process claims for payment. These requirements are intended to increase transparency and uniformity nationwide.

Comments and industry response

FDA's intended actions related to IVD regulation and the enactment of the Protecting Access to Medicare Act of 2014 are likely to result in substantial additional requirements for CLIA-certified laboratories and IVD manufacturers at all stages of product development. Industry should monitor carefully for FDA's proposed draft LDT guidance documents, which may be officially published on or after September 29, 2014. FDA likely will establish an open a public docket to accept comments at that time. Industry should also monitor for CMS rulemakings to implement the statutory reporting provisions, which are expected in the first half of 2015.

If you have questions about this *Client Alert*, please contact one of the authors listed below or the Latham lawyer with whom you normally consult.

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Endnotes

- ¹ FDA News Release, "FDA Takes Steps to Help Ensure the Reliability of Certain Diagnostic Tests" (Jul. 31, 2014), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm407321.htm>.
- ² See letters from Sally Howard, Deputy Commissioner, Policy, Planning and Legislation, FDA, to Tom Harkin, Chairman, Committee on Health, Education, Labor and Pensions & Fred Upton, Chairman, Committee on Energy and Commerce, House of Representatives (July 31, 2014), *available at* <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf>.
- ³ Pub. L. No. 112-144 § 1143, 126 Stat. 993.
- ⁴ See Citizen Petition to FDA, American Clinical Laboratory Association, FDA-2013-P-0667-0001 (June 4, 2013), *available at* <http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0667-0001>. This Citizen Petition was denied by FDA on July 31, 2014, the same day that it released its LDT notice. See Letter from Leslie Kux, Assistant Commissioner for Policy, Public Health Service, FDA, to Alan Mertz, President, American Clinical Laboratory Association (Jul 31, 2014), *available at* <http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0667-0008>
- ⁵ Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices (2014), *available at* <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>.
- ⁶ *Id.* at 7 (emphasis added).
- ⁷ *Id.* at 6.
- ⁸ *Id.* at 9.
- ⁹ *Id.* at 10.
- ¹⁰ *Id.* at 11.
- ¹¹ *Id.* at 12-13.
- ¹² *Id.* at 6.
- ¹³ Pub. L. 113-93, § 216 (2014) (codified at 42 U.S.C. § 1395m-1).