FDA's Draft Guidance on Laboratory Developed Tests ("LDTs") and *In Vitro* Diagnostic Devices ("IVDs") Marketed as LDTs by CLIA-Certified Laboratories[1, 2, 3]

Categories, Classes and Types of LDTs	LDT Notification Requested per the Draft *Framework* and *Notification Guidance*[4]	Device Establishment Registration & Device Listing per 21 C.F.R. Part 807[5]	Medical Device Reporting ("MDR") per 21 C.F.R. Part 803	Premarket Review per 21 C.F.R. Parts 803 and 814[6]	Quality System Regulations ("QSRs") in 21 C.F.R. Part 820	Jones Day Comments
Highest-Risk LDTs[7] • LDTs with the same intended use as cleared or approved companion-diagnostics[8] • LDTs with the same intended use as approved Class III medical devices • Certain LDTs used to determine the safety/efficacy of blood or blood products, most of which the Center for Biologics Evaluation and Research regulates	Within 6 months after publication of the final *Framework* for LDTs that were introduced before the final *Framework* ("existing LDTs") Prior to clinical use for LDTs introduced 6 or more months after publication of the final *Framework* ("new LDTs") When laboratories significantly change an LDT's intended use Laboratories should update LDT notifications when they make other significant changes to LDTs	A laboratory manufacturing one or more LDT and at least one other device would have to register as a device establishment and list each device, including each LDT A laboratory that manufactures only LDTs and submits timely LDT notifications and updates would have to: (i) register as a device establishment when FDA receives the laboratory's first LDT premarket submission; and (ii) list each LDT when FDA receives the first premarket submission for that LDT A laboratory that manufactures only LDTs and opts not to submit LDT notifications and updates within the applicable notification deadline for LDTs, would upon expiration of the earliest deadline have to: (i) register as device establishment; (ii) list each cleared or approved LDT, if any, under the product code identified in its clearance or approval letter; and (iii) list each noncleared or unapproved LDT for which LDT notification is requested (see below) under the product code "OQS"[9]	Six months after the publication of the final *Framework*, laboratories would have to comply with the manufacturers' MDR requirements set forth in Subpart E for LDTs they manufacture[10] The user facility MDR requirements in Subpart C would continue to apply to LDTs used by laboratories	FDA would require a premarket submission, e.g., a premarket approval application ("PMA") or a 510(k) premarket notification ("510(k)"): (i) within 12 months after publication of the final Framework for the existing Highest-Risk LDTs; and (ii) before initial clinical use for new Highest-Risk LDTs[11] FDA would continue to exercise enforcement discretion regarding existing Highest-Risk LDTs while the Agency is reviewing their premarket submissions if the laboratory sent them within 12 months after publication of the final *Framework*.	A laboratory would have to comply with QSRs when it submits a PMA or FDA clears a 510(k) for its LDT[12]	Highest-Risk LDTs would require premarket submissions before other types of LDTs Most of these LDTs would require the highest level of premarket review, i.e., PMA approval A laboratory's timely submission of LDT notification(s) for Highest-Risk/PMA LDTs would postpone registration and listing of the LDT for an additional six months

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Class III (high risk) LDTs[13]	Same as above	Same as above (the premarket submission for a Class III LDT would be a PMA and the PMA approval letter would identify its product code)	Same as above for both manufacturers and user facilities	FDA plans to identify the order and time frames for submission of PMAs for different types of Class III LDTs based on their risks compared to other Class III LDTs ("the Class III LDTs Priority List") within 24 months after publication of the final *Framework*[14] FDA would require the submission of PMAs for existing Class III LDTs sequentially by type based on the Class III LDTs Priority List starting 12 months after issuance of the list, i.e. 36 months after the publication of the final Framework if FDA issues the priority list by the 24-month deadline. FDA expects to complete its review of the PMAs for Class III LDTs within five years after publication of the final *Framework* FDA has indicated that the following thee categories of LDTs are likely to be the highest priority Class III LDTs: (i) devices that act like companion diagnostics; (ii) screening devices for serious diseases and/or conditions without any available confirmatory diagnostic product or procedure; and (iii) diagnostic devices for certain infectious diseases with high-risk intended uses A new Class III LDT would require PMA approval before its initial clinical use	Laboratories would have to comply with QSRs when a PMA is submitted for a Class III LDT FDA intends to increase the use of third party pre-approval inspections	FDA would regulate these LDTs before all but the Highest-Risk LDTs and would require the highest level of premarket review, i.e. PMA approval Class III LDTs, like the Highest-Risk LDTs that require PMA approval, would have to comply with QSRs upon submission of the PMA, but that event would occur 2 – 4 years later for the Class III LDTs

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Class II (moderate risk) LDTs	See above	Same as above (the premarket submission for a Class II LDT would be a 510(k) and the substantial equivalence letter would identify its product code)	Same as above for both manufacturers and user facilities	FDA plans to identify the order and time frames for submission of 510(k)s for different types of Class II LDTs based on their risks compared to other Class II LDTs ("the Class II LDTs Priority List") within 4 years after publication of the final *Framework* FDA would require the submission of 510(k)s for existing Class II LDTs sequentially by type based on the Class II LDT Priority List after the phased-in PMA review of Class III LDTs is complete. FDA expects the phased-in review of 510(k)s for Class II LDTs to begin 5 years and end 9 years after publication of the final *Framework* A new Class II LDT would require 510(k) clearance before its initial clinical use Third parties would review most 510(k)s	Laboratories would have to comply with QSRs once a 510(k) is cleared for a Class II LDT with a possible exception	Class II LDTs would require the lowest level of premarket review, i.e. 510(k)s, and only after FDA has reviewed premarket submissions for LDTs that present at least a high risk FDA seems to imply that a Class II LDT currently considered a Class I device or a Class II device that is exempt from 510(k) requirements would not have to comply with QSRs. It does not indicate whether it would create this exception by regulation or by exercising enforcement discretion

Categories, Classes and Types of LDTs	LDT Notification Requested per the Draft *Framework* and *Notification Guidance*[4]	Device Establishment Registration & Device Listing per 21 C.F.R. Part 807[5]	Medical Device Reporting ("MDR") per 21 C.F.R. Part 803	Premarket Review per 21 C.F.R. Parts 803 and 814[6]	Quality System Regulations ("QSRs") in 21 C.F.R. Part 820	Jones Day Comments
Class I (low risk) LDTs	Same as above	A laboratory manufacturing one or more LDT and at least one other device would have to register as a device establishment and list each device, including its LDTs, in accordance with the current regulations A laboratory that manufactures only Class I LDTs or other LDTs that are minimally regulated due to factors other than risk-based classification (see below) and submits timely LDT notifications and updates would not have to register as a device establishment or list those LDTs A laboratory that manufactures only LDTs and opts not to submit LDT notifications and updates by the applicable notification deadlines for LDTs would, upon expiration of the earliest such deadline, have to: (i) register as a device establishment (even if all its LDTs are Class I); (ii) list each of its cleared or approved LDTs, if any, under the product code identified in its clearance or approval letter; and (iii) list its noncleared or unapproved LDTs for which LDT Notifications are requested, including its Class I and/or minimally regulated LDTs, under the product code "OQS"[15]	Same as above for both manufacturers and user facilities	None, FDA would continue to exercise enforcement discretion	No, FDA would continue to exercise enforcement discretion and not require Class I LDTs to comply with QSRs	Class I LDTs would, at least initially, be subject only to minimal regulation (LDT notification or both establishment registration and device listing and MDR reporting). Laboratories manufacturing only LDTs that submit timely LDT notifications for their Class I LDTs would not have to register unless or until they manufacture another LDT subject to registration and listing However, FDA intends to exercise enforcement discretion with respect to 510(k) and QSR requirements rather than exempting them from such requirements by classification regulations. Thus, FDA may discontinue the exercise of enforcement discretion after "adequate notice"

Categories, Classes and Types of LDTs	LDT Notification Requested per the Draft *Framework* and *Notification Guidance*[4]	Device Establishment Registration & Device Listing per 21 C.F.R. Part 807[5]	Medical Device Reporting ("MDR") per 21 C.F.R. Part 803	Premarket Review per 21 C.F.R. Parts 803 and 814[6]	Quality System Regulations ("QSRs") in 21 C.F.R. Part 820	Jones Day Comments
LDTs that Would Be Minimally Regulated Due to Factors Other than Risk-Based Classifications **LDTs for Rare Diseases**[16] **Traditional LDTs**[17] **LDTs for Unmet Needs**[18]	Same as above	Same as above for Class I LDTs	Same as above for both manufacturers and user facilities	**LDTs for Rare Diseases:** FDA would continue to exercise enforcement discretion and not require 510(k) clearance or PMA approval for LDTs for rare diseases. FDA encourages, but would not require, laboratories to obtain approval of Humanitarian Device Exemptions under 21 C.F.R. Part 814, Subpart H for these LDTs **Traditional LDTs:** FDA would continue to exercise enforcement discretion and not require 510(k) clearance or PMA approval for this category of LDTs **LDTs for Unmet Needs:** FDA would continue to exercise enforcement discretion and not require 510(k) clearance or PMA approval for these LDTs unless or until the Agency clears or approves a device for the same indication. In that case, the laboratory would have to submit a PMA or a 510(k) for the device within 12 months of FDA's decision regarding the product cleared or approved for the same indication. FDA would exercise enforcement discretion while reviewing the submission for the LDT used for the previously unmet need.	It is not clear whether FDA would continue to exercise enforcement discretion and not require compliance with QSRs for any of the three categories of LDTs	These three categories of LDTs would be subject to the same minimal FDA regulation as Class I LDTs, assuming FDA's enforcement discretion extends to QSRs. However, FDA's enforcement discretion regarding premarket (and possibly QSR) requirements for LDTs for Rare Diseases or Unmet Need is conditional and thus could end if those conditions were no longer met

Categories. Classes and Types of LDTs	LDT Notification Requested per the Draft *Framework* and *Notification Guidance*	Device Establishment Registration & Device Listing per 21 C.F.R. Part 807	Medical Device Reporting ("MDR") per 21 C.F.R. Part 803	Premarket Review per 21 C.F.R. Part 807, Subpart E and Part 814	Quality System Regulations ("QSRs") in 21 C.F.R. Part 820	Jones Day Comments
Non-regulated LDTs LDTs used solely for forensic (law enforcement) purposes LDTs used in CLIA-certified, high-complexity histocompatibility laboratories for transplantation of organs, stem cells, and tissues (excluding LDTs used in HLA testing for blood transfusion)	FDA will continue to exercise enforcement discretion and not subject these types of LDTs to any LDT-specific or generally applicable device requirements					As noted above regarding Class I and other Minimally Regulated LDTs, FDA could discontinue enforcement discretion after adequate notice
Currently Regulated LDTs LDTs for Infectious Agents, i.e. donor screening tests used in blood and blood components and HCT/Ps Approved & Cleared LDTs	N/A	These LDTs must continue to comply with all of these device requirements				FDA could reclassify certain LDTs and thus increase or decrease regulation based on the Agency's experience with them

Lawyer Contacts

For further information, please contact your principal Firm representative or one of the lawyers listed below. General email messages may be sent using our "Contact Us" form, which can be found at www.jonesday.com.

Laurie A. Clarke
Washington
+1.202.879.3498
lclarke@jonesday.com

Colleen M. Heisey
Washington
+1.202.879.3449
cmheisey@jonesday.com

Brigid C. DeCoursey
Washington
+1.202.879.3651
bdecoursey@jonesday.com

Endnotes

1 This summary is based on the following two documents FDA released on September 30, 2014: (i) FDA's *Draft Guidance for Industry, Food and Drug Administration Staff and Clinical Laboratories: Framework for Oversight of Laboratory Developed Tests* ("the *Framework*"); and (ii) *Draft Guidance for Industry, Food and Drug Administration Staff and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory Developed Tests* ("*Notification Draft Guidance*"). FDA states on page 5 of the *Framework* "[l]aboratory tests that are being marketed as LDTs but are in fact not LDTs are out of compliance with the [Food, Drug, and Cosmetic] Act; however in the interest of ensuring continuity in the testing marketing and avoiding disruption of access to these tests, FDA intends to apply the same risk-based framework . . . [set forth in that document] to any IVD that is offered as an LDT by a CLIA-certified laboratory."

2 IVDs are tests that can detect diseases, conditions, or infections. Some tests are used in laboratory or other health professional settings and other tests are for consumers to use at home. As described by FDA, an LDT is a type of *in vitro* diagnostic test that is intended for clinical use and designed, manufactured, and used within a single laboratory. LDTs do not include devices designed or manufactured completely, or partly, outside of the laboratory that offers and uses them. LDTs were formerly called "home brews" and/or "in-house devices." Neither the *Framework* nor the *Notification Draft Guidance* apply to direct-to-consumer LDTs.

3 The *Framework* and *Notification Draft Guidance* state LDTs would be subject to any other applicable device requirements, e.g., correction and removal regulations in 21 C.F.R. Part 806. On page 27 of the *Framework*, FDA notes that the vast majority of clinical studies of IVDs currently are exempt from the investigational device exemption ("IDE") requirements in 21 C.F.R. Part 812 but FDA approval is required if it is a significant risk device as defined in 21 C.F.R. § 812.3(m). In addition, FDA asserts its authority to take enforcement action if necessary to protect the public health or to continue to exercise enforcement discretion when there are shortages of medically necessary LDTs or for other compelling reasons.

4 As proposed, LDT Notifications would include the following information: (i) the laboratory's name and contact information; (ii) the name of the test, its intended and clinical uses, and its monthly test volume; (iii) what the test measures, e.g., analytes, or detects, such as organisms; (iv) the disease or condition for which the LDT is indicated; (v) its intended patient population, including whether the LDT would be used on patients less than 21 years old; (vi) the sample types such as whole blood or urine; (vii) the test method; and (viii) whether the LDT is a modification of an already cleared or approved test, and, if so, a description of the modifications.

5 LDT laboratories would have to pay the annual device establishment registration user fee, which is $3,646 for Fiscal Year ("FY") 2015 (October 1, 2014 through September 30, 2015).

6 FDA user fees apply to premarket submissions for LDTs. For PMAs, the standard user fee is $250,895 for a PMA in FY 2015. For smaller business, if the company and its affiliates' gross sales or revenue for the previous year were less than $30 million, the user for its first PMA is waived; if its gross sales or revenue for the most recent tax year were less than $100 million, the reduced user fee is $62,754. The standard and small business user fees for 510(k) notices in FY 2015 are $5,018 and $2,509, respectively. LDT laboratories may voluntarily file premarket submissions.

7 FDA states the reason LDTs are not currently classified is owing to the Agency's exercise of enforcement discretion. FDA, however, has assigned product code OQS to LDTs.

8 A companion diagnostic device is an in vitro diagnostic device that provides information essential for the safe and effective use of a corresponding therapeutic product; the instructions for use for both the companion diagnostic and therapeutic product, as well as any generic equivalents, stipulate their combined use.

9 As of the date of this publication, FDA's Product Classification database states that "registering and listing is not required" for LDTs under product codes OQS. As of October 2, 2014, no devices are listed under that product code.

10 As of the date of this publication, FDA's Product Classification Database states that "the reporting of adverse events is voluntary" for LDTs under the OQS product code.

11 As of the date of this publication, FDA's Product Classification Database states "submission type: enforcement discretion" for LDTs under the OQS product code." As of October 2, 2014, FDA has not cleared or approved any LDTs under that product code.

12 As of the date of this publication, FDA's Product Classification Database indicates that LDTs under product code OQS are not exempt from Good Manufacturing Practices/Quality System Regulations.

13 FDA plans to issue a draft guidance classifying most LDTs into one of the following three risk-based classes within 18 months after the publication of the final *Framework*: Class I (low risk), Class II (moderate risk), and Class III (high risk). The Agency plans to finalize the LDT classification guidance within 24 months after the publication of the *Framework*. FDA plans to seek Advisory Committee input on the classification of LDTs.

14 The Class III PMA priority list presumably would be part of, or issued in conjunction with, the final LDT Classification Guidance.

15 As of the date of this publication, FDA's Product Classification database states that "registering and listing is not required" for LDTs under product code OQS. As of October 2, 2014, no devices are listed under that product code.

16 LDTs for Rare Diseases must meet the criteria for Humanitarian Use Devices in 21 C.F.R. § 814.102 , i.e. fewer than 4,000 persons in the United States would be diagnosed using the LDT per year.

17 FDA intends to determine whether an IVD is a traditional LDT based on whether: (i) the device meets the Framework's definition of an LDT, i.e. whether the device is designed, manufactured, and used by a single laboratory; (ii) the LDT is both manufactured and used by a health care facility laboratory (such as one located in a hospital or clinic) for a patient that is being diagnosed and/or treated at the same facility or within the facility's health care system; (iii) the LDT is comprised of only legally marketed components and instruments, e.g., analyte specific reagents (21 C.F.R. § 864.4020), general purpose reagents (21 C.F.R. § 864.4010), and various classified instruments; and (iv) the LDT is interpreted by qualified laboratory professionals without the use of automated instrumentation or software.

18 FDA intends to determine whether an IVD is an LDT for Unmet Needs based on whether: (i) the device meets the definition of LDT in this guidance, i.e. it is a device designed, manufactured, and used by a single laboratory; (ii) any FDA cleared or approved IVD for that specific intended use is available; and (iii) the LDT is both manufactured and used by a health care facility laboratory (such as one located in a hospital or clinic) for a patient that is being diagnosed and/or treated at the same health care facility or within that facility's health care system.