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# FDA PLANS TO REGULATE LABORATORY DEVELOPED TESTS AS DEVICES

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that a device is intended to treat, diagnose or cure. The direct final rule, which was published on 1 April 2010, was withdrawn on 19 July 2010.

**References**

1. *Federal Register*, 2010, **75**(138), 41986 (20 July 2010).
2. *Journal of Medical Device Regulation*, 2010, **7**(2), 41 (May 2010).

## FDA Plans to Regulate Laboratory Developed Tests as Devices

The Food and Drug Administration (FDA) announced plans for a public meeting on 19-20 July 2010 to discuss the Agency's intention to regulate laboratory developed tests (LDTs) as medical devices under the *Federal Food, Drug and Cosmetic Act* (FFD&C Act). The purpose of the meeting was to allow for public input on this new initiative. In the announcement for the meeting[1], the FDA stated that it intends to apply a risk-based approach to the regulation of LDTs, and following the meeting the FDA 'will move forward expeditiously to develop a draft oversight framework'. While the Agency has long asserted that it has jurisdiction over LDTs, it has not actively regulated most LDTs. It is possible that certain stakeholders will seek to challenge the FDA's authority to regulate LDTs on the grounds that LDTs do not fit within the definition of a 'device' under the FFD&C Act[2]. Even putting aside jurisdictional questions, how the FDA will apply its device authorities to LDTs raises numerous complex questions.

*Background*

LDTs are diagnostic tests that are developed, validated and performed by individual laboratories. They are sometimes referred to as 'home brews'. These assays are developed for in-house use and are not commercially distributed to other laboratories. Every day, hundreds of laboratories use LDTs to test for a wide variety of diseases and conditions. LDTs can be distinguished from commercially-available *in vitro* diagnostic (IVD) test kits, which are developed by diagnostic manufacturers and sold to clinical laboratories. For many diseases or conditions, commercial test kits are not available, and development of an IVD kit may not be commercially feasible. In addition, LDTs have often been developed to respond to public health threats (e.g. the H1N1 virus) where the delay inherent in obtaining FDA approval of a test could have had significant public health consequences.

Clinical laboratories that develop and use LDTs are currently subject to oversight and regulation under the *Clinical Laboratories Improvement Amendments of 1988* (CLIA)[3], which assigns primary responsibility for regulation of laboratories to the Centers for Medicare and Medicaid Services (CMS)[4]. Under CLIA, laboratories that offer LDTs must be certified to perform high-complexity testing. To be certified, the laboratory must permit inspection by the CMS, establish a quality assurance and proficiency testing programme, and comply with other requirements. CLIA also requires that laboratories validate LDTs to ensure that the results are accurate and reproducible. In addition, some state laws impose extra requirements on clinical laboratories. New York, for example, requires that all LDTs be approved by state authorities before they may be used in testing specimens from state residents.

The FDA's authority to regulate LDTs is less certain. Since at least the early 1990s, the FDA asserted that LDTs were medical devices that were subject to regulation under the FFD&C Act. However, the Agency declined to implement a comprehensive regulatory scheme for LDTs and instead announced an enforcement discretion policy. In addition, rather than regulating LDTs themselves, the FDA

promulgated a regulation in 1997 under which it regulates analyte specific reagents (ASRs), which serve as the building blocks of LDTs[5]. In recent years, however, the Agency has begun to assert some regulatory oversight over certain types of LDTs. In 2006[6] and again in 2007[7], the FDA issued draft guidance regarding IVD multivariate index assays (IVDMIAs), a subset of LDTs that diagnose high-risk diseases or conditions and that use complex algorithms to combine multiple inputs. Consistent with that guidance document, the FDA has cleared pre-market notifications (510(k)s) for several IVDMIAs. In addition, the FDA has recently issued letters to several companies that offer genetic testing services directly to consumers, requesting that these companies submit pre-market notifications or pre-market approval applications (PMA) for these tests[8].

Despite the fact that the FDA has asserted its regulatory authority over some types of LDTs, the vast majority of LDTs have continued to be offered without FDA oversight.

*FDA's Policy Shift*

In the announcement of its policy shift regarding LDTs, the FDA cited the evolution of LDTs from well understood pathology tests or tests for rare diseases and conditions to complex tests that 'are playing an increasingly important role in clinical decision-making and disease management, particularly in the context of personalized medicine'. In addition, the FDA said, 'even when FDA-approved tests are available for a disease or condition, laboratories often continue to use LDTs that have not been reviewed by the agency'. The FDA's concern is that 'LDTs that have not been properly validated for their intended use put patients at risk', including 'missed diagnosis, wrong diagnosis, and failure to receive appropriate treatment'.

In light of these concerns, the Agency determined that now is the time to reconsider its policy of enforcement discretion over LDTs. However, the Agency also referred to issues 'unique to the laboratory community' that would have to be taken into account in its regulatory framework for LDTs. In particular, the FDA noted that 'the field of genomics and genetic testing has the potential to revolutionize patient care', and its hope is to foster innovation in this area while assuring such tests are safe and effective. The FDA also noted the need to foster innovation in tests for rare diseases and conditions. The FDA stated its intent to 'provide a reasonable, predictable, and consistent regulatory policy for ensuring the safety and effectiveness of LDTs and provide sufficient time for implementation'.

While the Agency did not set forth a specific proposal in the meeting agenda, it did state that '[a]t this time, FDA believes that a risk-based application of oversight to LDTs is the appropriate approach to achieve the desired public health goals'. No further discussion was provided regarding this risk-based approach. Instead, the Agency convened the public meeting for stakeholders to present and discuss their views of the issues that present the greatest risk to public health.

The FDA's meeting announcement did not set forth a specific timetable for implementing a new LDT policy. Following the public meeting and the close of the public docket, the 'FDA will move forward expeditiously to develop a draft oversight framework for public comment to provide predictability as quickly as possible'. The FDA also intends to phase in such a framework over time based on the level of risk of the test, and has asked for public comment on 'the issues that pose the greatest concern to the public health'. The Agency did not indicate whether its LDT policy would be implemented by regulation or guidance

documents. The comment period for this public meeting closes on 15 August 2010.

*Questions Raised*

As an initial matter, there is significant chance that the FDA's policy will be challenged by stakeholders. In addition to the potential jurisdictional challenges, the FDA's announcement raises numerous questions, including (but not limited to) the following:

1. Will the Agency seek to promulgate device classification regulations for LDTs?
2. Will the Agency exempt certain categories of LDTs from pre-market notification? If so, what criteria will the FDA use to make such determinations?
3. Does the Agency expect that every laboratory provider will submit a 510(k) or PMA for each LDT offered? How will the FDA apply its usual safety and effectiveness approach of evaluating one analyte and one disease/condition in the context of the multiple analytes often involved in complex LDTs?
4. How will the FDA regulation be reconciled with regulation under CLIA? Will laboratories be subject to dual regulation under both CLIA and the FFD&C Act? Will separate proficiency testing and validation under CLIA still be required?
5. How will the FDA implement Quality System Regulation and Good Manufacturing Practice requirements for a clinical laboratory?
6. What is the status of the FDA's IVDMIA guidance document as a result of this policy shift? How will the FDA reconcile its initial steps to regulate LDTs that are IVDMIAs with its intentions to 'provide sufficient time for implementation' and to 'phase in' a regulatory framework over time for LDTs[9]?
7. What is the status of the FDA's recent actions regarding direct-to-consumer (DTC) genetic testing? Will these and other DTC LDTs be incorporated into the regulatory framework under this policy shift, or regulated under a separate and distinct framework?
8. Will the FDA continue to regulate ASRs? By directly regulating the finished devices (i.e. the LDTs), will regulation of ASRs become no longer necessary?

**References**


1. *Federal Register*, 2010, **75**(116), 34463 (17 June 2010).
2. The FFD&C Act defines a device (in relevant part) as 'an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any component, part, or accessory, which is … intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals'. FFD&C Act §201(h); 21 United States Code (USC) §321(h).
3. 42 USC §263a; Public Law No 100-578, 102 Statute 2903 (1988).
4. Pursuant to CLIA, the FDA has been assigned responsibility for complexity categorisation determinations for IVD devices. Title 42 of the Code of Federal Regulations (CFR) §493.17(c)(1)(i).
5. *Federal Register*, 1997, **62**, 62243 (21 November 1997). In promulgating the ASR rule, the FDA reiterated its view that FDA clinical laboratories that develop LDTs are 'acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act'. The FDA declined again to regulate LDTs, reiterating its enforcement discretion policy. The regulations governing ASRs are promulgated at 21 CFR §§809.10(e), 809.30 and 864.4020.
6. *Journal of Medical Device Regulation*, 2006, **3**(4), 54 (November 2006) and *Journal of Medical Device Regulation*, 2007, **4**(1), 83 (February 2007).
7. *Journal of Medical Device Regulation*, 2007, **4**(4), 63 (November 2007).
8. Various stakeholders disagree as to whether the FDA has the statutory authority to regulate LDTs. Several comments and citizen petitions have been submitted to the Agency arguing that

the FDA lacks the statutory authority to regulate LDTs as medical devices. See, for example, Docket No 2006-P-0402, Petition of Washington Legal Foundation. Others, however, have encouraged the FDA to regulate actively all LDTs, or at least certain types of high-risk LDTs. See, for example, Docket No 2008-P-0638, Petition of Genentech, Inc.

9. The Director of the FDA's Center for Devices and Radiological Health was quoted as saying that the Agency no longer intends to develop a final IVDMIA guidance in light of this new regulatory initiative. See *FDA to drop IVDMIA policy*, *BioCentury Extra*, **118**(114), 16 June 2010.

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## Guidance on Intravascular Stents and Associated Delivery Systems

A guidance document has been published that provides the Food and Drug Administration's (FDA's) current thinking on non-clinical engineering tests that are submitted in Investigational Device Exemption applications (IDEs) and Pre-Market Approval applications (PMAs) to support the safety and effectiveness of intravascular stents and their associated delivery systems. The guidance also provides recommendations for labelling for these devices. The document is entitled, *Guidance for Industry and FDA Staff - Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*, and was issued on 18 April 2010. It supersedes the guidance of the same name dated 13 January 2005.

This updated guidance document applies to self-expanding and balloon expandable extracranial intravascular stents and their associated delivery systems. The scope includes extracranial intravascular stents placed in coronary or peripheral arteries and saphenous vein grafts but is not limited to stents used in these locations; other vascular indications outside of the intracranial vasculature are also included. Intravascular stents, including balloon expandable and self-expanding stents, are Class III devices and require a PMA before marketing.

Clinical studies conducted in the USA in support of a PMA approval must be conducted under the IDE regulation (Title 21 of the Code of Federal Regulations Part 812). The FDA believes that the intravascular stents addressed by this guidance are significant risk devices and, as such, are not exempt from the requirement to submit an IDE application. When an IDE application is required, a sponsor must not begin a clinical trial in humans in the USA until the FDA has approved the application. After the FDA has approved a device, clinical studies conducted in accordance with the indications in the approved PMA, including clinical design validation studies conducted in accordance with the quality systems regulation, are exempt from the IDE requirements. However, such studies must be performed in conformance with the regulations governing Institutional Review Boards and informed consent.

Some of the tests (and labelling recommendations) in this guidance are relevant to covered, drug-eluting and biodegradable stents, and stents used to treat aneurysms or dissections. However, the FDA recommends additional testing to characterise fully these devices.

## Question and Answer Guidance on IVD Device Studies

The Food and Drug Administration (FDA) has prepared a comprehensive guidance document, written in a question and answer format, to address issues concerning *in vitro* diagnostic (IVD) studies[1,2]. The draft of this document was issued on 25