

COMPLIANCE PERSPECTIVES



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What Is The FDA Doing With Lab-Developed Tests?

Concern is growing among laboratories over the Food and Drug Administration's (FDA) recent move to begin treating laboratories developing and marketing some laboratory-developed tests (LDTs—also called “home brew” tests) as medical device manufacturers and requiring these labs to obtain FDA clearance or approval for these tests. What is going on? Will LDTs be subject to FDA regulation as medical devices in the future? First, some background on LDTs and regulation of these tests.

Two Pathways To Develop Lab Tests

Entities developing clinical laboratory assays choose the pathway they take to commercialization: (1) develop a product to sell to laboratories for their own use (in vitro diagnostic devices or IVDs) or (2) develop a clinical laboratory service provided solely by the laboratory developing the test (LDTs). The first pathway requires premarket submission to the FDA, the manufacture of the IVD is subject to FDA's Quality System Regulations (QSRs), and labeling and promotion are subject to various FDA requirements. The latter pathway has not required FDA premarket submission; the laboratories and the tests offered are subject to federal regulation under the Clinical Laboratory Improvement Amendments of 1988 (CLIA 88), plus state licensure requirements, and promotional claims are subject to the Federal Trade Commission's prohibition against false or deceptive advertising.¹

History Of FDA Regulatory Policy On LDTs

A 1992 FDA draft Compliance Policy Guide (CPG) stated that LDTs are medical devices. An October 1992 Citizen Pe-

tition responded by asking FDA not to regulate LDTs because such regulation would conflict with CLIA 88, is not authorized by the Federal Food, Drug, and Cosmetic Act (FFDCA), and would result in lower quality care. FDA denied the petition, in 1998, asserting that the agency has authority to regulate LDTs—an assertion never reviewed by the courts.²

In November 1997, FDA issued a final rule regulating “analyte-specific reagents” (ASRs)—the active ingredients of many LDTs. In the preamble to that rule, FDA reiterated its view that laboratories developing LDTs are medical device manufacturers. Nonetheless, the agency declined to regulate LDTs as medical devices: “FDA recognizes that the use of in-house developed tests has contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes in this area could have negative effects on the public health.”³ FDA also indicated that regulation of LDTs was not necessary because “regulating the active ingredients of in-house developed tests should provide an appropriate level of regulation to protect the public health.”⁴ Therefore, although FDA maintained that it had the authority to regulate LDTs, it also confirmed that it would not do so—to serve public health interests.

Fast Forward: Signs Of Change At FDA

In early 2006, several clinical laboratories offering highly innovative LDTs received letters from FDA inviting them to meet with the agency to discuss the nature and appropriate regulatory status of their tests and the least burdensome ways to fulfill any premarket review require-

¹ See, e.g., www.ftc.gov/os/2000/04/ehpattachmentb.htm

² A copy of the 1992 Citizen Petition and the FDA's response can be found at www.hpm.com/devitem.cfm?RID=74.0

³ 62 Fed. Reg. 62,243,62,249 (Nov. 21, 1997).

⁴ Id. at 62,252.

ments that may apply. The companies were stunned to learn that, despite years of clear agency policy supporting an LDT pathway under CLIA and outside FDA regulations, FDA was considering regulation of their tests as medical devices.

The apparent dramatic change in FDA enforcement policy raised numerous questions. Why these tests? What is the medical device? How can laboratories resolve conflicts between FDA regulations and CLIA and state laws that would still pertain to their premarket validation and postmarket services?

FDA Releases Draft Guidance: IVDMIAs

Responding to questions from stakeholders as to whether FDA was changing its long-standing policy of not regulating LDTs, FDA released a draft guidance⁵, In Vitro Diagnostic Multivariate Index Assays (IVDMIA), acknowledging confusion about the regulation of certain LDTs. In the draft guidance, FDA provided a definition of IVDMIAs: "IVDMIA is a test system that employs data, derived in part from one or more in vitro assays, and an algorithm that usually, but not necessarily, runs on software to generate a result that diagnoses a disease or condition or is used in the cure, mitigation, treatment, or prevention of disease."⁶ FDA believes IVDMIAs are medical devices.

FDA described IVDMIAs as having the following three characteristics:

1 Use clinical data (from one or more in vitro diagnostic assays and sometimes demographic data) to identify an algorithm;

2 Employ the algorithm to integrate the data points to calculate a patient-specific result;

3 The result cannot be interpreted by clinicians using prior knowledge of medicine without information from the test developer regarding clinical performance and effectiveness.

In discussions about the draft guidance, FDA indicated that an LDT can involve software, an algorithm, or be multivari-

ate without necessarily falling under the IVDMIA definition. FDA has provided some examples of IVDMIAs: (1) a microarray that predicts colon cancer recurrence based on an RNA expression pattern; (2) an assay that integrates quantitative results from seven immunoassays to obtain a qualitative "score" that predicts the risk of Alzheimer's disease; and (3) a test that integrates age, gender, and genotype (five genes) to diagnose cardiovascular disease.⁷

Why Is FDA Taking This Action?

In the draft guidance, FDA reiterated its position that clinical laboratories developing LDTs are medical device manufacturers, but FDA has declined to regulate them as such because it believed (1) FDA already regulates the primary ingredients of LDTs (ASRs, general purpose reagents and equipment, controls) and (2) clinical laboratories certified to perform high complexity testing under CLIA have the ability to use ASRs in test procedures. By contrast, FDA believes IVDMIAs include elements beyond these primary ingredients and are "not within the ordinary 'expertise and ability' of the CLIA high complexity laboratories that FDA referred to when it promulgated the ASR rule."⁸

FDA provided no explanation of the agency's conclusion that it has the legal authority to regulate IVDMIAs beyond the simple assertion that these tests fit the statutory definition of a medical device.

Implications For Laboratories

The consequences of FDA deciding that a laboratory's new assay is an IVDMIA are numerous and serious. As medical devices, IVDMIAs may be subject to premarket review, investigational device exemption regulations, and postmarket compliance requirements and limitations. FDA will assign IVDMIAs to one of the three classes to which all devices are assigned based upon a test's intended use(s) and the level of control FDA believes is necessary to assure safety and effectiveness. According to FDA, most IVDMIAs will be class II or III devices.

⁵ Issued September 7, 2006.

⁶ Id. at 3.

⁷ See presentation slides from Courtney Harper, Ph.D. at Professional Roundtable, November 30, 2006.

⁸ Draft IVDMIA Guidance at 3.

Class II devices typically require an FDA-cleared 510(k) premarket submission before commercialization. Class III medical devices require approval of a premarket approval application, typically requiring expensive, multi-year clinical trials to prove safety and effectiveness for each “intended use.”

Pending clearance or approval of an IVDMIA for any use, these tests would be considered investigational and subject to FDA’s human subjects investigation regulations.⁹ During this phase, tests must be labeled: “For Investigational Use Only.”¹⁰ A clinical study involving an investigational IVDMIA may require FDA approval of an investigational device exemption. Third-party payers are likely to deny coverage of tests with an “investigational” label.

In the draft guidance, FDA confirms that IVDMIAAs would be subject to QSRs and the Medical Device Reporting regulation. However, FDA provides essentially no explanation as to how clinical laboratories can conform those requirements to CLIA requirements other than a general assurance that the agency will work with laboratories to identify the least burdensome compliance pathway.

Many Questions—Few Answers Thus Far

The draft guidance raises numerous questions. The broad IVDMIA definition in the draft guidance could include many established tests that incorporate in vitro diagnostic information into algorithms used to inform diagnosis or management. These could range from relatively simple calculations, such as creatinine clearance, to more complex measurements, like triple or quadruple screening for neural tube defects.

In public presentations, however, FDA has assured stakeholders that it is focusing on a small number of highly novel assays. Yet, neither the draft guidance nor subsequent conversations with FDA have provided industry a clear standard for distinguishing between IVDMIAAs subject

to FDA regulation and other LDTs that FDA will not regulate.

Can a bright line boundary between FDA-regulated and not-regulated LDTs be articulated, or is it inherently a “we’ll know it when we see it” standard? The latter “standard” would likely result in too much uncertainty for investors, and payers would likely resist covering tests whose regulatory status is uncertain. This new policy could severely reduce the flow of capital directed to development of promising, innovative diagnostic innovations.

What elements of IVDMIAAs comprise the medical device subject to which FDA’s pre-market review, labeling and promotion, and QSR requirements apply? How are the operations of a single clinical laboratory to be separated into the “manufacture” of an IVDMIA device versus the use of that device by a clinical laboratory performing a test service? The draft guidance describes an IVDMIA as a whole “test system—a term also used under CLIA regulations—but FDA offers no guidance to harmonize the FDA and CLIA requirements, other than by saying that “test system” in the draft guidance is not linked with use of the same term in CLIA regulations.

FDA recommends that laboratories identify instances where they believe compliance with CLIA would fulfill requirements under the QSRs, but FDA does not acknowledge that the two regulatory frameworks may conflict. For example, CLIA puts an affirmative obligation on laboratories to update test information whenever changes occur that affect test results or interpretation of results.

By contrast, FDA limits the ability of device manufacturers to change labeling without prior clearance or approval by FDA. This may put laboratories in an untenable situation of trying to comply with CLIA’s affirmative requirement to keep referring physicians informed while, at the same time, complying with FDA limitations on dissemination of information beyond FDA-cleared labeling.

⁹ 21 C.F.R. Part 812.

¹⁰ 21 C.F.R. § 809.10(c)(2)(ii).

The process for adopting test improvements is not clear. Laboratories frequently update laboratory methods and processes. This is especially true in the area of infectious diseases, where new strains of infectious agents are identified or new resistance emerges, and in the area of genetic/genomic analysis, where new mutations and variations are identified. If formal clearance or approval from FDA is required before test changes can be adopted, tests will freeze at specific points in time. Physicians and patients will encounter long delays to have the access to essential information that LDTs have provided, while FDA has moved at its own pace in clearing new assays for the same clinical use.

The fundamental nature of the questions raised by the draft guidance and the substantial impact the proposed change in FDA policy could have on laboratories, treating physicians, and patients highlight the need for thorough, thoughtful, and public consideration of these issues—i.e., the type of policy-making record developed only through public meetings and notice-and-comment rule making.

Developing Story

The release of the draft IVDMIA guidance should mobilize stakeholders to consider what the requirements for LDTs should be under CLIA, FFDCa, or other regulatory frameworks in order to maintain the patient care and public health infrastructure assured historically by LDT capabilities. Various venues in which these issues have been raised and to which feedback should be provided include:

1 The IVDMIA draft guidance, which is open for public comment through March 5, 2007 (see docket at www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm [2006D-0347]).

2 Several stakeholders have asked FDA to hold a public meeting to discuss the draft guidance before it is finalized. FDA has not responded to these requests.

3 A Citizen Petition challenging FDA's authority to regulate LDTs or, in the alternative, arguing that FDA should proceed with regulation of LDTs only after

following proper notice-and-comment rule making was filed by the Washington Legal Foundation.¹¹ There is an open docket where interested parties can submit comments: www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm (2006P-0402).

4 A Citizen Petition was submitted to the Centers for Medicare & Medicaid Services (CMS), which administers CLIA, calling upon CMS to create a "genetic testing specialty" and establish regulations tailored to genetic testing laboratories under CLIA.

5 Senator Obama (D-IL) submitted "the Genomics and Personalized Medicine Act of 2006,"¹² aiming to improve access to and appropriate utilization of valid molecular genetic tests. The bill calls for a study to make recommendations to improve federal oversight and regulation of genetic tests, including genetic LDTs.

6 Senator Kennedy, who will be the chairman of the Senate Committee on Health, Education Labor and Pensions in the new Congress, is also considering legislative alternatives that potentially would make all LDTs medical devices regulated by FDA under the FFDCa.

The regulatory horizon for LDTs is much different at the close of 2006 than at the beginning. Although the exact form and timing of new regulation is unclear, some expansion in regulation of at least some types of LDTs is likely. Interested stakeholders have the opportunity to help shape whatever new regulatory framework may be put in place. Clinical laboratories, treating physicians, and patients all should become familiar with the IVDMIA draft guidance and the other legislative and regulatory proposals being circulated. Feedback to legislators and regulators to let them know how these proposals may affect the appropriate use of and reimbursement for diagnostic information used in clinical decision making is essential.

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¹¹ A copy of the petition may be found at: www.hpm.com/devitem.cfm?RID=74.0

¹² S. 3822 (submitted August 3, 2006).