

Checking In On FDA's Enforcement Discretion Policy for Laboratory Developed Tests

May 13, 2019

Key Points

- In a recent warning letter, the Food and Drug Administration (FDA) advised a laboratory to seek marketing authorization for its genetic tests that qualified as laboratory developed tests (LDTs)—which have largely benefited from enforcement discretion by FDA up to now.
- FDA's action evinces particular concern with the clinical validation of high-risk tests that purport to predict a drug response that may be inconsistent with FDA-approved drug labeling.
- Both the warning letter and recent attention to “cloud-based” labs demonstrate the limitations of the LDT designation for innovative test technologies.

Introduction

As Congress considers comprehensive reforms to the regulatory paradigm for all in vitro clinical tests (IVCTs), including LDTs, recent developments are highlighting the limitations of FDA's current posture of enforcement discretion.

- First, FDA is sufficiently concerned about certain types of LDTs that might lack clinical evidence supporting their claims that the agency issued a warning letter to the laboratory that developed and operated the test—indicating that the agency's policy of enforcement discretion is not absolute.
- Second, FDA's LDT policy may have limited applicability to “cloud-based” laboratory tests that operate using a software algorithm rather than traditional test methods.

Warning Letter

On April 4, 2019, FDA issued a warning letter to a health system laboratory, instructing it to stop marketing its MediMap pharmacogenetic tests absent FDA marketing authorization.¹ The laboratory marketed five MediMap tests as genetic tests for predicting medication response, reducing negative side effects from certain medications, discovering the right drug and right dose for a patient, and avoiding trial-and-error prescribing by health care providers by testing patient receptivity to drugs that treat specific conditions. FDA expressed concern about whether data existed to

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establish the relationship between genotypes assessed by the tests and assertions regarding drug response for multiple drugs.

In FDA's view, these claims make the tests medical devices that are subject to FDA jurisdiction under the Food, Drug and Cosmetic Act (FDCA)—meaning that the laboratory would typically need to obtain FDA's premarket authorization to market the tests, but it had not. However, these particular tests are considered LDTs, a category of tests that have largely gone unregulated by FDA. At the same time, FDA updated a safety communication jointly issued by FDA's Center for Drug Evaluation and Research (CDER) and the Center for Devices and Radiological Health (CDRH) in October 2018 that warned consumers about genetic tests that purport to predict patients' responses to specific medications.² The two Centers jointly issued a statement regarding the warning letter,³ signaling broad agency support for the advisory action.

FDA's History of Enforcement Discretion for LDTs

Clinical laboratories have historically developed "home brew" tests for use within their own laboratories. Although FDA has asserted jurisdiction over these tests, the agency has generally exercised enforcement discretion as long as they were developed and used within an individual certified laboratory. Over the last decade, however, the rapid proliferation and increasing complexity of LDTs have prompted FDA to attempt to assert active regulatory oversight of these tests. FDA issued draft guidance in 2014 in which the agency reiterated its statutory authority over LDTs and proposed a risk-based framework.⁴ Under the proposed framework, certain high-risk LDTs would have been subject to premarket review, Quality Systems requirements, Medical Device Reporting for adverse events and malfunctions, and registration and listing requirements.⁵ Other lower-risk tests would have continued to be subject to enforcement discretion for most device requirements—so long as they met the agency's definition of an LDT: "in vitro diagnostic that is intended for clinical use and designed, manufactured, and used within a single laboratory."⁶

FDA has not finalized the draft guidance, and in the midst of policy discussions surrounding the appropriate regulatory framework for LDTs, issued a discussion paper in 2017, which echoed a similar message but suggested a somewhat different regulatory approach.⁷ Given the lack of a formalized policy, the draft guidance still stands as the most recent articulation of the agency's interpretation of what constitutes an LDT that is generally eligible for enforcement discretion.

Of particular importance here, the warning letter did not question that MediMap tests qualified as LDTs. According to the letter, "Although FDA has generally exercised enforcement discretion for LDTs, the Agency always retains discretion to take action when appropriate. . . ."⁸ Warning letters for LDTs have been quite rare, so this serves as a reminder that FDA's limited enforcement does not mean zero enforcement or advisory action.

High-Risk Nature of Laboratory's Conduct

The laboratory's tests in this case presented particularly high risks in FDA's view, and thus served as a vehicle through which the agency could highlight the safety and effectiveness concerns related to certain LDTs, particularly genetic tests for which the agency believes there is insufficient clinical evidence.

Three aspects of the laboratory's activities likely contributed to FDA's decision to issue a warning letter:⁹

- Lack of clinical validity, including for treatment recommendations that contradicted approved drug labeling.
- Provision of the test results directly to patients.
- The laboratory's refusal to implement changes in response to FDA's initial communications.

Following the issuance of the warning letter, the laboratory stopped offering the tests.¹⁰

Lessons for Test Developers

Although the warning letter may signal a greater willingness to enforce in the LDT space generally, the facts in this particular case made these tests especially ripe for agency attention. The warning letter and associated safety warning do not necessarily mean that all developers of laboratory tests face heightened enforcement risk, but laboratories and test developers may consider ways to limit their exposure to risk.

The letter indicates that FDA is concerned about two types of tests: (1) tests that have not been validated, but that recommend medications in a manner *consistent* with the drug's FDA-approved labeling; and (2) tests that have not been validated and recommend medications in a manner that is *inconsistent* with the drug's FDA-approved labeling.

For both types of tests, conducting studies to establish the test's clinical and analytical validity would limit risk exposure. The first situation, in which tests are consistent with approved drug labeling, is inherently less risky, and conducting validation studies would generally be less burdensome. For example, in the case of next-generation sequencing tests, the criteria set forth for establishing clinical validity for cleared or approved tests are instructive. For tests that share biomarkers with already authorized tests, a test developer could document comparisons to authorized tests with the same biomarkers. To demonstrate clinical validity, a test maker may rely on publicly available clinical evidence, such as professional guidelines and/or peer-reviewed publications, i.e., the test maker does not necessarily need independently to establish clinical validity.¹¹ Documentation that the test works effectively to identify the genotype and that the laboratory relied on the scientific community's clinical evidence would work to lower the risk level.

The second type of test, one that analyzes biomarkers for which clinical validity has not been well established or produces results that may be inconsistent with FDA-approved labeling, is viewed as particularly high risk by the agency. Indeed, the agency has informally raised concerns with other such LDTs that lack marketing authorization. Developers of such tests would face a greater challenge: documenting that the test works as intended and that there is clinical evidence to support recommendations for off-label uses of medications. Nevertheless, developers are less likely to face enforcement action if they conduct and document internally the testing to support these claims.

In addition, sending test information directly to patients might invite increased agency attention. FDA is concerned that test results could lead patients to adjust dosing inappropriately or stop medication completely without physician involvement, which

may cause significant risks to patient safety. Compounding this factor in the warning letter, one of the cited tests provided medication recommendations for newborns.

In the event a laboratory's tests do draw agency attention, the laboratory will often have the opportunity to engage with the agency before a warning letter is issued. Absent immediate public health concerns, such as adverse events, FDA often makes a practice of contacting a firm informally before issuing a warning letter. In this case, FDA requested that the laboratory change the tests and labeling to address the agency's concerns, including by removing labeling regarding drug responses for specific medications unless and until FDA reviewed information to support the claims and granted marketing authorization. The laboratory responded to FDA that the tests qualified as LDTs and were therefore not subject to premarket review. FDA then issued the warning letter.

Cloud-Based Laboratories

The lack of clear policy from FDA regarding LDTs has also presented a challenge for companies that purport to conduct LDTs from a laboratory based in the cloud. For example, some tests run algorithms in a cloud-based laboratory. Such tests could theoretically meet FDA's last-articulated definition of an LDT: in vitro diagnostic intended for clinical use and designed, manufactured and used within a single laboratory. However, in FDA's 2014 draft guidance, FDA defined a "single laboratory" to mean a facility with a single Clinical Laboratory Improvement Amendments of 1988 (CLIA) certificate for high-complexity testing from the Centers for Medicare and Medicaid Services (CMS).¹²

At the moment, cloud-based facilities that do not analyze physical specimens are not currently required to register with CLIA. Even if they do register, however, it is not clear that cloud-based laboratories could meet the standards required to obtain a CLIA certificate due to their inherent limitations as virtual laboratories. It is also unclear whether FDA would adhere to the criterion in the 2014 draft guidance that limits its policy of enforcement discretion to laboratories with such high-complexity certification. Of course, FDA never finalized the 2014 Draft Guidance, and as a result, there is no official FDA position defining the scope of LDTs.

A recent Clinical Laboratory Improvement Advisory Committee (CLIAC) touched on whether and, if so, how, CMS should regulate cloud-based laboratories and CMS is expected to issue guidance on this topic. In addition, proposed legislation, the Verifying Accurate, Leading-edge, IVCT Development Act (VALID Act), would establish a new regulatory framework for LDTs and other in vitro clinical tests. A broad group of stakeholders, including the American Clinical Laboratory Association, AdvaMedDx, the Biotechnology Innovation Organization and Friends of Cancer Research, recently sent a letter to the Senate Health, Education, Labor and Pensions (HELP) Committee and House Energy & Commerce Committee to urge lawmakers to finalize changes to the proposed legislation by the end of the year.¹³ Given that FDA's enforcement efforts in this area are not completely dormant, test developers of cloud-based laboratories would greatly benefit from bright-line clarity from Congress, CMS and FDA.

1 FDA, Warning Letter to Inova Genomics Laboratory (Apr. 4, 2019), available at [Inova Genomics Laboratory - 577422 - 04/04/2019](#) [hereinafter "Genetic Test Warning Letter"].

2 FDA, Safety Communication, The FDA Warns Against the use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication (issued Oct. 31, 2018);

updated Apr. 4, 2019), *available at* https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm624725.htm?utm_campaign=2019-04-05%20CDRH%20New&utm_medium=email&utm_source=Eloqua.

3 FDA, FDA Issues Warning Letter to Genomics Lab for Illegally Marketing Genetic Test That Claims to Predict Patients' Responses to Specific Medications (Apr. 4, 2019), *available at* <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm635283.htm>.

4 FDA, Draft Guidance, Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) (Oct. 3, 2014), *available at* <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm416685.pdf>.

5 *Id.*

6 *Id.* at 5.

7 FDA, Discussion Paper on Laboratory Developed Tests (LDTs) (Jan. 13, 2017), *available at* <https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/UCM536965.pdf>.

8 Genetic Test Warning Letter.

9 *Id.*

10 GenomeWeb, Inova Decides to End PGx Test Offerings in Response to FDA Warning Letter (Apr. 15, 2019), *available at* <https://www.genomeweb.com/regulatory-news/inova-decides-end-pgx-test-offerings-response-fda-warning-letter#.XNHzaI5KiUk>.

11 See FDA, Fact Sheet: CDRH's Approach to Tumor Profiling Next Generation Sequencing Tests, *available at* <https://www.fda.gov/media/109050/download>.

12 FDA, Draft Guidance, Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) 5 n.5 (Oct. 3, 2014), *available at* <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm416685.pdf>. (providing that a single laboratory refers to a facility with a single CLIA certificate as described in 42 C.F.R. § 493.43(a)-(b) and 42 C.F.R. § 493.55 and that meets the requirements outlined in 42 C.F.R. §§ 493.17(c)(4) and 493.25).

13 Letter from American Cancer Society Cancer Action Network, Friends of Cancer Research, American Clinical Laboratory Association, AdvaMedDx, and other stakeholders to Sens. Alexander, Murray and Reps. Pallone and Waldern (May 3, 2019), *available at* <https://www.acla.com/wp-content/uploads/2019/05/Diagnostics-Reg-Reform-Stakeholder-Ltr-to-Hill-5-3-19.pdf>.

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