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INSIGHT

HHS Announcement on FDA Premarket Review of Laboratory-Developed Tests (LDTs)

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Regulation of laboratory-developed tests (LDTs)—a class of in vitro diagnostic (IVD) device that is designed, manufactured, and used within a single laboratory—by the Food and Drug Administration (FDA) has been the subject of ongoing discussion, driven in part by an increase in the number and complexity of LDT genetic tests for common conditions. FDA has traditionally exercised enforcement discretion over LDTs, meaning that most of these tests have neither undergone premarket review nor received FDA clearance or approval for marketing. To date, FDA has focused its oversight on IVD test kits or components, which are commercially marketed as opposed to developed and carried out in a single laboratory. In recent years, despite the absence of broader agency guidance on the regulation of LDTs, FDA has asserted authority over certain LDTs that it considers to be higher risk.

HHS Announcement

On August 19, 2020, the Department of Health and Human Services (HHS) announced that, effective immediately, it was rescinding all guidance, compliance manuals, website statements, or other informal issuances concerning FDA premarket review of LDTs. The announcement applies to all LDTs—including COVID-19 LDTs—and states that FDA may not require premarket review for these tests absent a notice-and-comment rulemaking process. Per the announcement, premarket review includes premarket approval (PMA), premarket notification (510(k) notification), and Emergency Use Authorization (EUA). HHS notes that laboratories may *voluntarily* submit an EUA request, PMA, or 510(k) for LDTs.

FDA responded to this change in policy in early October, noting that it would "declin[e] to review EUA requests for LDTs at this time," including new EUA submissions and those already in the process of being reviewed. In response, HHS directed the agency to review all voluntarily submitted EUA applications for COVID-19 LDTs, noting that submissions will be referred to the National Institute of Health's National Cancer Institute for review if the FDA's timeframe for review exceeds 14 days. Therefore, clinical laboratories may *voluntarily* submit EUA applications for COVID-19 LDTs to FDA—and FDA must review them—but FDA may not *require* submission of such applications absent rulemaking.

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FDA Regulation of LDTs During a Public Health Emergency

The FDA has maintained that it has clear regulatory authority over LDTs, as it does with all in vitro diagnostics (IVDs) that meet the definition of medical device in the Federal Food, Drug, and Cosmetic Act (FFDCA), although it has not generally enforced requirements for LDTs. LDTs that are developed for and used during a public health emergency have usually not come under the auspices of this exercise of enforcement discretion, and FDA has stated previously that these LDTs should not be used clinically without approval, clearance, or authorization from the agency. The EUA process is usually used to expedite access to medical products during an emergency that would otherwise require premarket approval. However, because premarket requirements for LDTs are generally waived through enforcement discretion by the agency, the EUA represents additional regulatory requirements for the clinical use of an LDT in an emergency. In contrast, for commercial test kits, the EUA represents an abbreviated review mechanism that allows the unapproved product to be used during an emergency without undergoing the full FDA premarket review typically required.

FDA Regulation of COVID-19 Diagnostics

Numerous COVID-19 tests have received EUA, allowing for their marketing and clinical use during the COVID-19 emergency with abbreviated review and data requirements. Through guidance dated May 11 (initially published February 29), FDA allows for modifications to the usual EUA process to facilitate a more rapid scale-up of testing. Specifically, FDA allows certain COVID-19 diagnostics—both LDTs and test kits—to be manufactured and used clinically *prior* to EUA authorization, but *after* test validation and agency notification. For molecular and antigen tests, the guidance allows laboratories and commercial manufacturers to perform and manufacture their tests prior to receiving EUA, as long as they validate the test, notify FDA, and submit EUA materials within 15 days. For serology tests, manufacturers (but not clinical laboratories developing LDTs) have 10 days to submit EUA materials to the agency, and may similarly manufacture and distribute their test in the interim after validation and agency notification. During the pendency of agency review, tests are to be performed only in high complexity clinical laboratories; upon EUA authorization, a test may be carried out in settings specified in the Letter of Authorization, including high or moderate complexity laboratories or waived settings (for use at the point-of-care).

Issues for Consideration

The HHS announcement clarifies that entities using an LDT that is not approved, cleared, or EUA authorized would not be eligible for coverage under the Public Readiness and Emergency Preparedness (PREP) Act, which provides certain liability protections for covered persons administering covered medical countermeasures. Clinical Laboratory Improvement Amendments (CLIA) requirements apply to clinical laboratories using LDTs, irrespective of a test's EUA or approval status.

Several issues are raised by the HHS announcement and its accompanying FAQ, including, but not limited to the following:

- The announcement does not provide a definition for LDT, raising possible questions about the scope of its applicability.
- The announcement does not note if, and if so to what extent, other FDA regulatory requirements—for example, postmarket requirements—may apply to LDTs.
- It is not clear how or if this change in policy will apply to requests for modifications of EUA authorized LDTs (e.g., adding a new sample type).
- Coverage of COVID-19 diagnostics pursuant to requirements in the Families First Coronavirus Relief Act (FFCRA) may be affected by this new policy. The requirements

- apply to COVID-19 IVDs that are FDA approved, cleared, authorized for marketing pursuant to *de novo* classification, or EUA authorized. In addition, the statute requires coverage of tests that are being used clinically or marketed per state authorization or in the interim between notifying the FDA of test validation and the agency granting EUA, pursuant to FDA guidance. It is unclear whether LDTs being used without EUA (or state authorization or pursuant to agency notification) would similarly be required to be covered under FFCRA requirements.

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