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Beth Weinman

Gregory Levine

Michael Purcell

Pandemic May Spur Reform Of Lab Test Regulation

By **Beth Weinman, Gregory Levine and Michael Purcell**

April 7, 2020 - On March 5, a bipartisan group of legislators introduced the Verifying Accurate, Leading-edge IVCT Development, or VALID, Act of 2020 in both the U.S. House of Representatives and Senate.[1]

The bill seeks to create a framework for U.S. Food and Drug Administration regulation of a new category of medical products known as in vitro clinical tests. This product category would include both laboratory-developed tests, or LDTs, and other in vitro diagnostic tests.

While not a new issue, the current COVID-19 emergency may reenergize the push for LDT-related legislation.

In a press release announcing the introduction of the legislation, the House bill's sponsor, Rep. Diana DeGette, D-Colo., blamed the existing regulatory framework for dramatic shortages in coronavirus testing kits and framed the legislation as a means of avoiding future delays in responding to public health emergencies.[2] DeGette specifically echoed complaints by public health officials that FDA policy requiring premarket review of LDTs was impeding prompt diagnosis of potential COVID-19 cases in the U.S.[3]

Coronavirus Testing and LDTs

On Jan. 31, U.S. Department of Health and Human Services Secretary Alex Azar declared the COVID-19 outbreak to be a public health emergency pursuant to the Public Health Service Act. This declaration allowed the FDA to begin granting emergency use authorization under the Federal Food, Drug and Cosmetic Act for unapproved diagnostic tests and other medical products necessary to address the crisis. Even so, the demand for COVID-19 tests has far exceeded the available supply.

On Feb. 29, the FDA implemented a new policy to speed the availability of diagnostic testing by allowing laboratories certified to perform high-complexity testing under the Clinical Laboratory Improvement Amendments to use tests they develop and validate to diagnose COVID-19 even before the FDA issues an emergency use authorization for

their test.[4] The new policy makes clear that, following validation, laboratories have a "reasonable period of time" — interpreted by the FDA as 15 business days — to submit emergency use authorization requests to the agency after they begin using the test in patients.

The FDA updated and expanded this guidance on March 16, to include a policy for commercial test kit manufacturers analogous to the policy announced for CLIA high-complexity laboratories in the Feb. 29 guidance. The update also stated that the FDA would not object to a state choosing to authorize laboratories within the state to develop and perform a test for COVID-19, even if those laboratories do not apply to the FDA for an emergency use authorization, provided that the relevant state "takes responsibility for COVID-19 testing by laboratories in [the state] during the COVID-19 outbreak."[5]

FDA's Role in LDT Regulation

As DeGette's comments quoted above make clear, the need for a clinical laboratory to obtain FDA authorization to market a test it develops and validates has been the subject of ongoing debate. In 2014, the FDA issued draft guidance announcing that it would end its historical policy of enforcement discretion regarding LDTs — in existence since the passage of the Medical Device Amendments in 1976 — and outlining the first of multiple frameworks that have been proposed for their regulation.[6]

In its draft guidance, the FDA explained the dramatic changes in the LDT landscape that it believed justified increasing agency oversight over LDTs, which, in its view, met the statutory definition of "devices."[7]

Specifically, the guidance noted that LDTs were no longer primarily made by small, local laboratories; no longer primarily relied on the manual techniques of laboratory personnel; and were no longer primarily used and interpreted by physicians and pathologists who worked in a single institution responsible for the patient for whom a diagnosis would be made. In addition, LDTs were increasingly being made from components that were not legally marketed for clinical use.[8] Further, LDTs increasingly required complex, high-tech instrumentation and software to generate results and clinical interpretations; and guided critical clinical management decisions for high-risk diseases and conditions, particularly in the context of personalized medicine.[9]

Though many patient advocates, providers, laboratories and diagnostics manufacturers have expressly recognized that oversight structures for clinical laboratory diagnostics must be modernized,[10] some have pushed back against the agency's announced intention to regulate LDTs by arguing that such regulation falls outside of the FDA's jurisdiction.[11]

Throughout, the FDA has maintained its position that it can regulate LDTs as devices and, with regard to public health emergencies specifically, has considered it critical that the agency review a laboratory test's design, validation and performance characteristics.[12] As former FDA Commissioner Scott Gottlieb recently explained via Twitter, in the event of a public health emergency, diagnostic tests "not only diagnose serious or life-threatening disease that's not completely understood, but help guide analyses of disease progression and risks to public health. … False negative results can have significant adverse consequences."[13]

VALID Act Regulatory Framework

The VALID Act of 2020 builds on years of efforts to grapple with questions surrounding LDT regulation. Like a previous draft of proposed legislation, the new proposed legislation seeks to amend the Federal Food, Drug and Cosmetic Act to create a comprehensive risk-based framework for the regulation of a new category of medical products — in vitro clinical tests, or IVCTs — overseen by the FDA's Center for Devices and Radiological Health.

The bill's new framework would establish, among other things, notification and listing requirements for IVCT developers as well as premarket review requirements (including a technology certification pathway previously referred to as precertification), IVCT labeling requirements, test design and quality requirements, and the required reporting to the FDA of corrections, removals, and adverse events.

The bill also outlines conditions for emergency use and multiple exemptions from the established framework review, such as for certain components and parts, grandfathered tests, low-risk tests, manual tests, and tests for rare diseases. Beyond this, the legislation would create a "Comprehensive Test Information System" to serve as a publicly available electronic database and one-stop shop for information about all marketed IVCTs.

The proposed legislation also provides for a program to accredit qualified entities and persons outside the FDA to review test applications and conduct inspections of IVCT developers. It also includes a detailed user fee program to fund all aspects of LDT regulation, not just premarket review.

Compared to a previous iteration of this legislation, the VALID Act includes several new or modified features, including:

- Elimination of the potential for duplication of Clinical Laboratory Improvement Amendments requirements for any regulated IVCTs;

- Modification of the definition of "high risk" with respect to an IVCT to mean that "an undetected inaccurate result" from such a test "presents potential unreasonable risk for serious or irreversible harm or death to a patient or patients, or would otherwise cause serious harm to the public health or is potentially likely to result in the absence, delay, or discontinuation of life-supporting or life sustaining medical treatment";

- Clarification of exemptions for "low-risk" LDTs as well as those that are intended for use in diagnosing rare diseases and those that are considered "grandfathered";

- Modification of the definition of "valid scientific evidence" to include real-world data;

- Regulation of "specimen receptacles," as IVCTs "specifically intended for the holding, storing, or transporting of specimens derived from the human body or for in vitro examination";

- Establishment of a mechanism for early consultation with the FDA to determine the appropriate regulatory pathway for an LDT;

- Establishment of a process and standards by which a "technology certification" (referred to as precertification in the 2018 draft legislation) can be granted to a group of similar eligible IVCTs falling within the scope of the certification that would exempt such IVCTs from premarket review during the period in which the certification is effective. An application for technology certification must be limited to a single technology, must include notification to the FDA for every IVCT the applicant intends to offer under the scope of the certification, and specified information concerning one or more representative IVCTs, including the test with the greatest analytical complexity at the time of filing;

- Establishment of a new streamlined review process allowing data submitted as part of the legislation's contemplated full and abbreviated premarket review processes to be used to support "technology certification" and deeming of a representative test submitted as a basis for a technology certification order as "approved" under the premarket review requirements;

- Establishment of premarket review requirement for otherwise exempt tests if (1) "there is insufficient valid scientific evidence to support the analytical validity or the clinical validity" of the IVCT; (2) the IVCT "is being offered by its developer with materially deceptive or fraudulent analytical or clinical claims"; (3) it is "reasonably possible" that the IVCT "will cause serious adverse health consequences;" or (4) with respect to "specimen receptacles, "there is sufficient valid scientific evidence indicating that a specimen receptacle did not perform as intended, will not support the analytical validity of tests with which it is used, or as applicable, is not safe for use";

- Modification of the provisions governing when changes made to a test will render such a test a "new IVCT" that might require separate approval, and the route by which modifications can be made;

- Addition of significant detail regarding (1) the "Comprehensive Test Information System" contemplated as an electronic database used both for premarket submissions and to house information about marketed tests, including adverse event information; (2) a comprehensive user fee program governing all regulation of IVCTs; (3) the process for accrediting third parties to assist with premarket review and inspections;

- Addition of previously absent deadlines throughout the bill, and modification (typically shortening) of deadlines included in the prior version;

- Elimination of the authority to ban an IVCT;

- Provision of a longer transition period such that most new authorities will only take effect on the first day of the fourth fiscal year after the date of enactment of the act, though the

secretary is required to hold required public meetings, promulgate regulations, and issue guidances required under the legislation before that time.

Conclusion

Many have expected that Congress would not address LDT reform legislation in a meaningful way until 2022, when the Medical Device User Fee Amendments and Prescription Drug User Fee Act programs were due for reauthorization.[14] The COVID-19 outbreak has potentially changed that expectation, however.

As of March 5, identical versions of the VALID Act had been introduced in both houses of Congress with support from individual members of both parties. The VALID Act's sponsors are highlighting the significant delay in the availability of COVID-19 diagnostics as an illustration of the critical and immediate need for a complete overhaul of the regulatory framework for in vitro diagnostics. Whether that argument moves this complex legislation forward in an accelerated time frame remains to be seen.

Beth Weinman is counsel, Gregory Levine is a partner and Michael Purcell is an associate at Ropes & Gray LLP.

[1] The revised bipartisan bill was introduced by U.S. Reps. Larry Bucshon, R-Ind., and Diana DeGette, D-Colo., in the House and U.S. Sens. Michael Bennet, D-Colo., and Richard Burr, R-N.C., in the Senate.

[2] See DeGette Press Release, available at https://degette.house.gov/media-center/press-releases/lawmakers-introduce-legislation-to-expand-nation-s-diagnostic-testing (last visited March 13, 2020).

[3] Id.

[4] Policy for Diagnostics Tests for Coronavirus Disease-2019 during the Public Health Emergency,available at https://www.fda.gov/media/135659/download (last visited March 23, 2020).

[5] Id.

[6] See Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories – Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs),available at https://www.fda.gov/media/89841/download (last visited March 14, 2020).

[7] See id.; See also Federal Register notice announcing availability of draft guidance, 79 Fed. Reg. 59776, 59777-78 (Oct. 3, 2014).

[8] Id.

[9] Id.

[10] See, e.g.,ACLA Letter from Industry Stakeholders on Diagnostics Regulation Reform,available at https://www.acla.com/letter-from-industry-stakeholders-on-diagnostics-regulation-reform/ (last visited March 23, 2020).

[11] See American Clinical Laboratory Association ("ACLA") White Paper, available at https://www.acla.com/wp-content/uploads/2015/01/Tribe-Clement-White-Paper-1-6-15.pdf (last visited March 14, 2020) According to the ACLA paper, Congress gave regulatory authority over LDTs to CMS in the Clinical Laboratory Improvement Amendments of 1988 (CLIA), which amended the Public Health Service Act.

[12] See, e.g. Untitled Letter to Viracor-IBT Laboratories, dated Oct. 21, 2016, available at https://www.fda.gov/media/100842/download (last visited March 24, 2020); It Has Come to Our Attention Letter to MD Biosciences, dated March 4, 2016, available at https://www.fda.gov/media/96214/download (last visited March 24, 2020)

[13] See Scott Gottlieb (@ScottGottliebMD), Twitter, (Feb. 24, 2020, 9:11 AM), https://twitter.com/ScottGottliebMD/status/1231944758261665795.

[14] In technical drafting recommendations to the 2018 draft of the VALID Act, HHS recommended that sponsors "[align] the authorization time frame [for the VALID Act] with the reauthorizations for MDUFA and PDUFA programs, which would allow them to be included in a single legislation." See Technical Assistance on VALID Act of 2018, at 17, available at https://www.documentcloud.org/documents/5991340-HHS-VALID-TA-20190405-Final.html (last visited March 20, 2020).