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Brief: Background and Summary of Diagnostic Test Reform and the VALID Act

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Several members of Congress are pursuing legislation that would establish a new regulatory framework at the Food and Drug Administration (FDA) for all diagnostic tests whether developed by a laboratory (LDTs) or by *in vitro* diagnostic (IVD) manufacturer (currently regulated as medical devices). The overall goal of this effort is to level the playing field among products, foster innovation, and give patients and providers greater certainly about the analytical and clinical validity of tests.

Background

In 2014, after years of exercising enforcement discretion over LDTs and efforts to move on a subset of LDTs (i.e., certain algorithmic tests referred to as "in vitro diagnostic multivariate assays"), FDA released a draft comprehensive guidance document detailing how it would begin to regulate such tests as medical devices. This proposed framework, and the notion of regulating through guidance, was met with strong opposition from Congress and the laboratory community. In 2016, at the end of the Obama Administration, the agency announced that it would not move forward with the guidance.

During this time, Congress began to explore whether FDA's regulation of all diagnostic tests—both LDTs and IVDs—should be modernized based on their unique attributes compared to traditional medical devices. Draft legislation, known as the Diagnostic Accuracy and Innovation Act (DAIA), was released by Reps. Diana DeGette (D-CO) and Larry Bucshon (R-IN) and circulated to stakeholders for several rounds of feedback in 2016 and 2017. Both the House and Senate held hearings on the topic. In April 2018, FDA responded by raising a number of concerns and followed up in August—via providing "technical assistance" (TA)—with new legislative language that differed quite significantly from DAIA.

By this point in time, Reps. DeGette and Bucshon had partnered with Senators Michael Bennet (D-CO) and Orrin Hatch (R-UT) on this legislative effort. In December 2018, they joined with then-Chairman of E&C Greg Walden (R-OR), now Ranking-Member, and then-Ranking Member Frank Pallone (D-NJ), Now Chairman, in releasing a new "discussion draft" titled the Verifying Accurate, Leading-Edge, IVCT Development (VALID) Act, which integrates in many respects FDA's proposal from August. Feedback on the VALID Act was requested by February 15, 2019.

VALID Act Overview

While borrowing many concepts from the Food, Drug and Cosmetic Act (FDCA), the VALID Act would establish a new framework under the FDCA for the review and oversight of in vitro clinical tests (IVCTs) separate and distinct from the medical device framework. It would not change or modify the Clinical Laboratory Improvement Amendments (CLIA) program. The framework aims to assure that IVCTs on the market provide a reasonable assurance of analytical and clinical validity.

VALID Act Scope

An IVCT under this new framework would be defined as a test that is "*intended to be used in the collection, preparation, analysis, or in vitro clinical examination of specimens for the purpose of identifying, diagnosing, screening, measuring, detecting, predicting, prognosing, analyzing, or monitoring a disease or condition, or selecting, monitoring or informing therapy or treatment for a disease or condition*." This definition includes test protocols, test platforms, specimen collection articles, and a component or part of a test, unless the component or part is intended for further development of an IVCT.

While not excluded from the definition of IVCT, many types of tests would not be subject to certain requirements of the new framework:

- Public health surveillance tests and law enforcement tests, would be exempt from all requirements.
- Tests for rare diseases (fewer than 8,000 individuals per year in the U.S. subject to such IVCT), manual tests, low-risk IVCTs[1], and IVCTs within the scope of a developer's precertification would be exempt from premarket review. (See below for explanation of precertification.)
- Single patient and low-volume (< 5 patients) tests would be exempt from premarket review, QS requirements, and notification requirements.
- Grandfathered tests (LDTs first marketed 90 days or more before enactment) would be exempt from premarket review, QS requirements, and labeling requirements subject to certain authorities maintained by FDA to act and modifications necessitating submissions to the FDA

VALID Act Regulatory Framework

Notification/Listing IVCT developers would be required to annually register with FDA, submit notification information with descriptions of each IVCT they offer (i.e., notification elements[3]), and be subject to inspection. Notification information would be posted on FDA's website.

Premarket review High-risk tests[4] would be subject to premarket review, as would companion diagnostics and first-of-a-kind tests[6]. The content of an application required for such tests would be similar to what is currently required for a PMA, including quality system and manufacturing information along with a description of the test's intended use, an explanation of

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[1]Low-risk IVCTs are those where an undetected inaccurate result would cause minimal or no harm or disability, or immediately reversible harm, or would lead to only a remote risk of adverse patient or public health impact; or would cause non-life threatening injury or injury that is medically reversible, or delay unnecessary treatment and mitigating measures are sufficient to prevent, detect or otherwise sufficiently mitigate the risk associated with such inaccurate result.

[3] Notification elements, which also define a "test group" for purposes of risk classification and modifications, include:

(A) Substance or substances measured by the IVCT, such as analyte, protein, or pathogen;
(B) Type or types of specimen or sample;
(C) Test method;
(D) Test purpose or purposes, such as screening, predicting, or monitoring;
(E) Diseases or conditions for which the IVCT is intended for use;
(F) Intended patient populations; and
(G) Context of use

[4] High-risk IVCTs are those where an undetected inaccurate result would likely cause serious or irreversible harm or death to a patient or would otherwise cause serious harm to the public health. Mitigating measures can be established to avoid a high-risk classification. FDA and IVCT developers can establish "mitigating measures" to avoid the high-risk classification, which can involve labeling, advertising, website posting of information, testing, clinical studies, post-market surveillance, user comprehension studies, training, conformance to standards, and performance criteria.

[6] A first-of-a-kind test is one which has a notification element or elements that differ(s) from the combination in any other legally available test group.

the tests function and performance, a risk assessment, and demonstration of compliance with any mitigating measures and standards. Raw data would typically be required. The application could also include a change protocol with validation procedures and acceptance criteria for any anticipated modifications that could be made without triggering a new application. Priority review, which would essentially afford a developer the current benefits of the breakthrough device pathway, would be available for tests that must go through premarket review and which provide or enable more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions compared to existing alternatives.

Precertification The stated intent of the FDA's proposal is that most tests would be exempt from premarket review[7] as most tests would be classified as low-risk or could be legally marketed pursuant to a "precertification order" granted to the test developer—assuming the developer avails themselves of this newly established, voluntary option. However, in addition to high-risk tests not being eligible for precertification, platforms, components and parts, IVCTs that are first-of-a-kind, test systems for home use, cross-referenced tests, and DTC tests would typically be ineligible as well.

Under this voluntary pathway, an eligible entity would submit an application that proposes the scope of the requested precertification order. The scope must be limited to a single technology (i.e., test method) but could include multiple medical subspecialties (not defined) and eligible entities could hold multiple precertification orders. If an order is granted, FDA would consider all tests the developer offers within the scope of the order to meet the standard of a reasonable assurance of analytical and clinical validity, while only reviewing a representative test(s). All other tests under the order would be reported to FDA through the notification requirements.

A precertification application would include information on one or more representative tests, including the highest complexity test, which has been validated within the developer's proposed scope, and an explanation of how such test(s) adequately represent the range of tests to be covered by a precertification order. The information required to be submitted for a representative test is similar in nature to the content of a premarket submission, including procedures for analytical and clinical validation.

An initial precertification order expires after two years. Subsequent renewals shall expire four years after the date the order is renewed. Applications for renewal must include information on a representative test that is different from any prior application.

As precertification is voluntary on the part of the developer, a developer of an IVCT that is eligible for precertification could decide to forego this pathway and submit a test-specific premarket application. In that instance, a streamlined process is established whereby such an application need not include QS documentation or raw data or undergo preapproval inspection.

Use of 3rd parties FDA would be permitted to use non-federal government agencies and qualified nongovernment organizations as third-party reviewers of applications for

[7] Commissioner Gottlieb noted in December that FDA anticipates under their proposal that only around 10 percent of tests will need premarket review. He also estimated that between 40 and 50 percent of tests would qualify for precertification.

precertification and applications for premarket review and make recommendations to FDA with respect to such applications.

Modifications The proposed framework allows modifications to IVCTs if the modification does not change any of the notification elements, performance claims or safety, performance, or compliance with mitigating measures or restrictions. Such modifications must be reported on an annual basis. Other modifications require a supplemental application.

QSR Developers must establish and maintain a quality system. A developer that operates its own CLIA-certified high-complexity laboratory where its tests are for use only within that certified laboratory, such a quality system must consist of design controls; purchasing controls, including supplier controls; acceptance activities; corrective and preventative action; and records. Separate requirements apply to high-complexity laboratories that distribute test protocols to other entities.

Adverse Event Reports Adverse events that have caused or contributed to a death or serious injury via malfunction that cannot be directly attributed to laboratory error must be reported to FDA within 5 days of a developer becoming aware of such event. All other adverse events are to be reported quarterly.

Post-market surveillance FDA may require post-market studies as a condition of approval, as part of a mitigating measure, or when necessary to meet the relevant standard or mitigate patient harm.

Corrections and Removals A developer must have processes for corrections and removals (i.e., recalls). Within 10 days of correction or removal of an IVCT, a developer must report to FDA if the action was taken to reduce the risk to health or to remedy a violation of the law.

Transition to the VALID Act Framework

Tests that were offered, sold, or distributed prior to enactment that have been regulated as medical devices would be deemed approved under the new IVCT framework upon the date of enactment. IVCTs that were first offered after enactment but prior to the effective date would be required to comply with device regulations. For tests with device applications pending on the effective date, FDA could continue to rely on the device authorities when acting upon a submission.

Transitional IVCTs are tests developed by a certified high-complexity lab for testing within that laboratory that are first offered during the period that is 90 days before enactment and the effective date. Such tests could continue to be offered until the effective date though FDA could rely on device authorities if necessary to protect the public from a serious risk to health. Transitional IVCTs with premarket or precertification applications pending on the effective date could continue to be offered during the review.

Test platforms that were purchased prior to enactment and have not been review by FDA may continue to be used by the purchaser for test development and clinical offering for 5 years after the date of enactment. At that point, any new IVCT that is developed and offered must be based on a platform that has been reviewed by FDA.