CENTER FOR Science IN THE Public Interest

The Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2021

Laboratory-developed tests (LDTs) are a type of in vitro clinical test (IVCT) that are developed and used in a single laboratory, distinguishing them from other IVCTs that are used by multiple laboratories and conventionally manufactured as medical devices.[1] LDTs are "send out" tests, meaning a sample is collected in one facility and sent to another to be tested, instead of collecting and testing a sample in the same facility.[2] Reliable LDTs are crucial, as inaccurate tests can lead, on the one hand, to failure to diagnose critical diseases or conditions and, on the other, to inappropriate treatment.

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), the Food and Drug Administration (FDA) has the authority to review medical devices, including LDTs, to ensure they are safe and effective before they are marketed.[3] However, to date FDA has not used this authority to regulate LDTs, allowing the devices to flow freely onto the market without premarket approval.

While the Verifying Accurate Leading-edge IVCT Development Act of 2021 (S.2209 and H.R.4128) (VALID) is presented as a solution to this problem by establishing a risk-based framework for regulating all IVCTs, regardless of where they are produced and used, the current version of the bill unfortunately paves a legal pathway to market for many of these tests without ensuring their accuracy. Without changes, the framework proposed under VALID will continue to enable the marketing of unsafe and untested LDTs, with potentially devastating consequences for consumers.

Inaccurate LDTs are a growing problem and may lead to misdiagnoses of common diseases.

In the 1970s, there were a limited number of LDTs and they were generally used to diagnose rare diseases and conditions in a small number of patients.[1] Advances in science and technology have enabled greater availability and complexity of tests that can be used to diagnose serious medical conditions like cancer, heart disease, and more recently, COVID-19.[1] The field of medicine is evolving, including a new focus on Precision Medicine, which tailors disease prevention and treatment to individuals by accounting for individual factors like genetic variation.[1] Development of accurate and clinically meaningful tests is crucial to support these advances.

In the absence of FDA oversight, labs offering LDTs are regulated by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments

(CLIA).[4] CMS regulates labs themselves, including the process of testing, rather than the safety and effectiveness of tests. CMS requires labs to have documentation of their tests' analytical validity, which determines if a test can detect the target of interest reliably. CMS does not require clinical validity data, that is the accuracy with which tests identify a particular disease or susceptibility to a disease in a patient. For example, if a blood test measuring proteins shed by pancreatic cancer cells is used to diagnose pancreatic cancer, CMS would only assess whether the test accurately detects the proteins, not whether the detection of the proteins is a reliable way to diagnose pancreatic cancer. By contrast, if LDTs were reviewed as medical devices, clinical and analytical validity would be assessed by the FDA, which would carry out a more comprehensive assessment with a focus on test safety and effectiveness prior to reaching patients.[1] Regulating LDTs under the CLIA, rather than by FDA, therefore leaves critical gaps that allow inaccurate LDTs to be marketed to consumers without adequate independent oversight. And examples of inaccurate LDTs abound.

In 2015, the FDA published a report that presented 20 case studies of problematic LDTs that caused or may have caused real harm to patients.[1] In some cases, patients were told they had conditions they did not have (false-positives); in others, patients' life-threatening conditions were not identified (false-negatives). The biomarkers measured in other tests had no proven relevance to the diseases that tests claimed to detect, or their associated treatments. The case studies included tests for a variety of conditions, such as Lyme disease, vitamin D deficiency, autism, fetal genetic abnormalities, heart disease, and various types of cancer.[1] The situation has only been exacerbated since the report was published, with many more LDTs being developed and used on an increasing number of patients, all without premarket review.[5] Some additional recent examples follow.

Prenatal tests

- Genetic non-invasive prenatal screening (NIPS) tests analyze small pieces of fetal DNA in the maternal circulation to assess the risk for genetic abnormalities in a fetus.[6] All are LDTs that are widely used by providers.[6] These are screening tests, but patients have terminated their pregnancies based on test results without further diagnostic testing.[6] Although companies claim their tests are highly accurate, some genetic abnormalities like microdeletions are so rare that false positives are common (they have low "positive predictive values").[6] FDA recently released a safety communication warning patients and providers about the risks of inaccurate results from NIPS tests.[6]

Theranos blood tests

- The company claimed it could deliver cheap and convenient tests, which were LDTs, to diagnose common conditions like diabetes, cancer, and cardiovascular disease using a single finger prick and a few drops of blood.[7,8] It capitalized on the LDT loophole, allowing it to circumvent FDA regulation and market tests that were inaccurate. For example, unreliable results led one consumer to believe she was HIV+ when she was not, and another was informed she was miscarrying when she had a healthy pregnancy.[9,10] Luckily, both women retested with different providers and learned the

truth, but these results could have led to unnecessary treatment for HIV or the termination of a healthy pregnancy.

COVID-19 tests

- In February 2020, FDA allowed COVID-19 diagnostic tests (which were LDTs) to remain on the market until FDA had a chance to review their applications for emergency use authorization.[11] By eluding review under the EUA provision, these LDTs were in essence regulated like all LDTs – without premarket review. The agency subsequently discovered validation or design issues in over 65% of a sample of 125 tests submitted for authorization.[11] Inaccurate results from these tests may have led to unnecessary quarantining due to false positives or to additional virus spread due to false negatives.

VALID aims to improve the regulation of LDTs by creating a new regulatory framework for all IVCTs.

FDA is aware of the public health risks posed by unregulated LDTs and has proposed regulation in the past. In 2014, it released a draft guidance[3] that outlined a risk-based approach to premarket review of LDTs and a process for notifying FDA of such tests. This elicited a strong response from industry and pressure from Congress led FDA to suspend work on its proposed regulation.[12] In 2017, the agency released a discussion paper[13] that synthesized stakeholder feedback on the draft guidance but made clear it would not implement this policy change through its current authorities, leaving it to Congress to address the issue. Then, in August 2020, the U.S. Department of Health and Human Services (HHS) revoked FDA's authority to evaluate the accuracy of all LDTs in an announcement on its website.[14,15] HHS has since reversed this decision, but has not proposed a new framework for regulation.[16]

Negotiations around LDT regulation resulted in the introduction of the VALID Act in 2020,[17] which was revised and reintroduced in 2021.[18] The bill has been modified and included in legislation that reauthorizes user fees for drugs, biologics, and devices (the Food and Drug Administration Safety and Landmark Advancements Act of 2022, "FDASLA"),[19] which is "must pass" legislation because these fees fund a substantial portion of FDA's regulatory activity.[20] VALID amends the FD&C Act to create a uniform regulatory framework for all IVCTs, including both LDTs and non-LDT IVCTs that are currently regulated as medical devices. The legislation includes a tiered approach to premarket review for the tests, as follows:

1. **Full premarket review:** Individual high-risk tests, or those where an undetected inaccurate result has a "substantial likelihood" of resulting in serious or irreversible harm or death to patients or is reasonably likely to result in the absence or delay of life-supporting or life-sustaining treatment, must undergo premarket review of their proposed labeling, submit raw data showing the test meets the applicable standard ("a reasonable assurance of analytical and clinical validity for its intended use, and a reasonable assurance of safety for individuals who come into contact with such IVCT"), and submit quality requirement (QR) documentation.

2. **Abbreviated premarket review: "**Moderate-risk" tests require review of only the proposed labeling and summary data demonstrating the test meets the applicable standard. No QR documentation or raw data are required unless the latter are requested by the Secretary. Moderate-risk tests include:
    a. High-risk tests with measures to prevent or detect an inaccurate result; or
    b. Tests where an inaccurate result would only cause non-life-threatening or medically reversible injury or significant delay in necessary treatment
3. **Exempt from premarket review:** IVCTs that qualify as exempt do not undergo any premarket review. These exemptions are wide-ranging and include:
    a. Low-risk tests (those where an undetected inaccurate result would cause minimal or immediately reversible harm with only a remote risk of harm to patients);
    b. Custom tests (those used to diagnose a unique condition for which no other IVCT is available);
    c. Low volume tests; and
    d. Grandfathered tests (those on the market prior to the bill's enactment)

Technology certification: In addition to the tiers described above, eligible developers of moderate- or low-risk tests may seek a technology certification order to develop and modify tests within a single technology type or fixed combination of technologies without individual review of each test. A developer must submit information to show that eligible tests within the scope of the certification will meet the applicable standard, including information showing that covered tests will conform to the applicable quality requirements, procedures for analytical and clinical validity, and procedures for establishing that tests are safe. FDA would individually review a representative test to confirm that the application of these procedures meets the applicable standard. "First-of-a-kind tests," unless determined to be eligible by the Secretary, and high-risk tests are ineligible for technology certification.

Special Rule: FDA can only require grandfathered tests on the market prior to enactment of the bill to undergo the premarket review process if (i) there is "insufficient valid scientific evidence" to support the test's analytical or clinical validity, (ii) the test makes misleading claims about validity, or (iii) it is "probable" that the test "will cause serious adverse health consequences." Going forward, the Special Rule does not apply to tests that are exempt from review or enter the market under an abbreviated review or technology certification.

The tiered approach to review exempts most tests from premarket review, including commercial IVCTs that are currently regulated as medical devices, shifting the majority of test oversight to the postmarket without providing appropriate authority or funding for such activities. Under VALID, postmarket regulation includes:

1. **Postmarket surveillance:** FDA can require developers of moderate- or high-risk tests to conduct postmarket surveillance if failure of the test to meet the applicable standard "is reasonably likely to result in serious adverse health consequences or death."

2. **Adverse event reporting:** A developer must submit a report to the Secretary if it receives information that reasonably suggests its test "may have caused or contributed to an adverse event." A developer must submit (i) individual adverse event reports when a test may have caused a patient death or presents an imminent public health threat within 5 days, and (ii) quarterly reports that include all test errors and serious injuries.

Some elements of the tiered approach in VALID are reasonable. However, significant deficiencies will leave patients exposed to harmful misdiagnoses due to inaccurate tests. CSPI recommends the following changes to address these shortcomings:

1. ***Clarify definitions and limit opportunities to evade premarket review.***

- The definition of high-risk uses a standard for harm resulting from treatment delays that is too narrow ("delay of life-supporting or life-sustaining treatment"), and would exclude, for example, treatment delays resulting in permanent disability.
    - **Recommendation: The definition of high-risk should be modified to remove "life-supporting or life-sustaining" and read: "[an undetected inaccurate result from such test, when used as intended] is reasonably likely to result in the absence, significant delay, or discontinuation of *necessary* medical treatment *resulting in serious or irreversible harm or death*." This would align the language for harm resulting from treatment delays with the language currently used for other harms caused by test errors, which includes "serious or irreversible harm or death."**
- The definition of moderate-risk leaves a gap where tests may be unable to be classified because they fail to meet the criteria for any risk category. For example, a test for which an inaccurate result could lead to serious or irreversible harm but there is not "substantial likelihood" of such a result would not meet the definition of a moderate-, high-, or low-risk test.
    - **Recommendation: The moderate-risk definition should be modified to include all tests that are neither high- nor low-risk.**
- Technology certification may lead to the development of multiple generations of products that are dissimilar in application to the original representative test. It may also allow a technology to be used for multiple indications without additional FDA review, including indications entirely distinct from the original certification, for which clinical validity has not been established.
    - **Recommendation: Technology certification should be modified by:**
        - **Requiring all tests within a technology certification order to not differ significantly in their indication or analytical and clinical validity;**
        - **Giving FDA the authority to define the circumstances in which a developer could receive a technology certification that covers multiple technologies through regulation or guidance; and**

- **Allowing FDA to request retrospective review of the data supporting analytical and clinical validity of tests developed under technology certification (discussed further *infra*).**

2. *Require retrospective review of high-risk grandfathered tests.*

- Countless grandfathered tests will be exempt from premarket review when many may not have undergone rigorous testing and/or may be high-risk.
    - **Recommendation: Developers of high-risk grandfathered tests should be required to undergo retrospective premarket review. At present, the burden is on the FDA to demonstrate that certain conditions are met (see above) before it can implement review of grandfathered products.**

3. *Enhance postmarket review.*

- FDA is only allowed to require postmarket surveillance for moderate- and high-risk tests if the failure of such test is "reasonably likely to result in serious adverse health consequences or death." This requires the agency to provide evidence establishing that a safety risk exists *before* it can order surveillance to collect such evidence, a difficult burden that may prove impossible to meet in many cases. By contrast, FDA may require postmarket surveillance under its existing authority to regulate medical devices whenever the agency determines such review is "necessary to protect the public health or to provide safety or effectiveness data."[21]
    - **Recommendation: FDA must have the authority to require postmarket surveillance for any test – not just moderate- and high-risk tests – when the agency determines that such review is "necessary to protect the public health or to provide data supporting analytical or clinical validity," language that is aligned with the standard for requiring postmarket surveillance of devices.**
- Submitting an adverse event report requires the developer to affirm that the test "may have caused or contributed to an adverse event," creating opportunity for the developer to avoid reporting, and exposing the developer to legal liability if they do report.
    - **Recommendation: Adverse event reporting should be required for all adverse events that are "associated with the use" of the developer's test, not just those where the developer determines that its test may have caused an adverse event.**
- The retrospective review of grandfathered tests allowed under the Special Rule is more restricted than FDA's authority over other devices because it gives the agency the high burden of demonstrating that a test is ineffective before it can request that the developer provide data establishing the test's efficacy. This standard runs counter to the advice

offered by FDA in the agency's technical assistance response, which advised that the Special Rule be replaced by a requirement that test developers document a test's validity, safety, and the truthfulness of claims, and provide this documentation to the agency on request.[22] The Special Rule also applies only to grandfathered tests, and does not allow FDA to investigate questionable tests that enter the market under technology certification or another exemption.

- **Recommendation: Change the Special Rule to allow FDA to review any test that has been exempted from premarket review, not just grandfathered tests. In addition, in line with the FDA's advice, test developers should be required to maintain, and provide to the agency on request, documentation establishing the basis for any claimed exemption from premarket review, as well as valid scientific evidence to support its determination that the test is analytically and clinically valid, data supporting any analytical or clinical claims made for the device, and data establishing that the test will not contribute to serious adverse health consequences.**

4. Provide additional funding to FDA.

- New Congressional appropriations are not authorized, the use of user fees is limited to premarket review activities, and FDA cannot collect such fees until after it has developed regulatory guidance, which requires time and resources.
    - **Recommendation: Include a mechanism for funding the activities required under VALID through authorizing additional appropriations, removing restrictions on the collection of user fees, or a combination of the two.**

For more information, please contact the Center for Science in the Public Interest at policy@cspinet.org.

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May 2022