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September 28, 2020

The Honorable Diana DeGette
U.S. House of Representatives
Washington, DC 20515

The Honorable Larry Bucshon, M.D.
U.S. House of Representatives
Washington, DC 20515

The Honorable Richard Burr
U.S. Senate
Washington, DC 20510

The Honorable Michael Bennet
U.S. Senate
Washington, DC 20510

Dear Representatives DeGette and Bucshon, and Senators Burr and Bennet:

Thank you for your continued efforts to streamline the regulation of clinical testing through the Verifying Accurate Leading-edge IVCT Development (VALID) Act. The Pew Charitable Trusts is an independent, nonpartisan research and policy organization with a longstanding focus on the quality and safety of medical products, including research and policy analysis on issues related to the regulation of *in vitro* diagnostics (IVDs).

The COVID-19 pandemic has highlighted the critical role that high-quality diagnostics play in mounting public health mitigation strategies and delivering timely and effective treatment. It has also underscored the need for Congress to prioritize comprehensive diagnostics reform that creates a uniform, risk-based regulatory framework that applies to all tests. The current system—in which tests are regulated according to where they are developed and used—exposes patients to unnecessary risk, and creates an uneven playing field for test developers. The recent decision by the Department of Health and Human Services to exclude laboratory-developed tests from premarket review by the Food and Drug Administration (FDA)—a decision which only increases regulatory uncertainty for developers—offers still further evidence that the current regulatory paradigm needs to change.[1]

While certain provisions in VALID may require additional consideration, the introduced bill represents continued progress toward the creation of a uniform regulatory structure that will better serve the interests of providers and patients. Unlike the current fragmented regulatory structure, VALID's framework would better ensure that tests are accurate and reliable, and would better match regulatory oversight to the risks those tests pose to patients.

[1] Assistant Secretary for Public Affairs (ASPA), "Rescission of Guidances and Other Informal Issuances Concerning Premarket Review of Laboratory Developed Tests," U.S. Department of Health & Human Services, last modified September 1, 2020, https://www.hhs.gov/coronavirus/testing/recission-guidances-informal-issuances-premarket-review-lab-tests/index.html.

In a previous comment, we proposed a series of principles that should guide any evidence-based approach to reform in this area.[2] While we are pleased to see several of these principles reflected in the introduced legislation, certain key provisions in VALID fail to appropriately balance mechanisms to enable rapid innovation with those that ensure public health safety, which could undermine the FDA's ability to oversee this market. As you refine the legislation, we urge you to consider the following recommendations:

1. Though the regulatory framework created by VALID is largely risk-based, the legislation exempts broad categories of tests from premarket review, including all tests currently on the market. Several of these exemptions should be more narrowly defined to ensure that patients are not placed at undue risk.
2. The bill introduces a new regulatory pathway called technology certification, which if enacted, would be a substantial departure from the FDA's traditional approach to review. Given the potentially broad scope of this untested pathway, as well as the many unresolved questions about how it will work in practice, a phased approach—or even a pilot program—will allow the FDA and Congress to better evaluate the benefits of this type of review structure.
3. Given the proportion of tests that would be exempt from premarket review under the VALID legislation, FDA's postmarket authorities will be critical to protecting public health. In particular, the FDA's authority under the Special Rule must not be hampered, and adverse event reporting needs to be improved.
4. The legislation must provide adequate resources for the FDA to effectively oversee this market. As currently written, VALID does not authorize appropriations, and would require the agency to achieve certain milestones—such as guidance development and rulemaking, all of which require significant time and resources—before being able to collect any user fees.

Exemptions from premarket review should be risk-based and carefully defined

VALID would transform the oversight of IVDs, moving away from the current fragmented system towards a uniform regulatory framework, which will better ensure the analytical and clinical validity of tests on the market and give patients more assurance that they can trust the results of their tests. However, the bill exempts several broad categories of tests from premarket review, some of which raise concerns. If not structured appropriately, categoric exemptions from review can lead to serious risks. The current pandemic has only underscored this fact. In response to the overwhelming need for new tests to identify people who had been exposed to the coronavirus, the FDA briefly allowed certain serology tests—which were intended to identify people with COVID-19 antibodies—to come to market without receiving an Emergency Use Authorization.[3] Within weeks, the agency had to reverse course, after receiving numerous reports

[2] E. Jungman, "Pew Comments on FDA's Response to Diagnostic Accuracy and Innovation Act," The Pew Charitable Trusts, August 20, 2018, https://www.pewtrusts.org/en/research-and-analysis/speeches-and-testimony/2018/08/20/pew-comments-on-fdas-response-to-diagnostic-accuracy-and-innovation-act.

[3] A. Shah and J. Shuren, "Insight into FDA's Revised Policy on Antibody Tests: Prioritizing Access and Accuracy," U.S. Food and Drug Administration, last modified May 4, 2020, https://www.fda.gov/news-events/fda-voices/insight-fdas-revised-policy-antibody-tests-prioritizing-access-and-accuracy.

of unreliable serology tests for sale.[4] This only underscores the need for Congress to exercise caution when granting broad premarket exemptions.

In general, such exemptions should only be applied in cases where the costs associated with premarket review—in terms of both time and resources—outweigh the benefits to public health. Thus, exempting custom or low-volume tests might make sense, as the risks these tests pose to public health are relatively low when compared to the benefits of making them available to patients more quickly. However, some of the exemption categories defined in VALID are overly broad, and the benefits to public health of relaxing premarket requirements are less clear.

Of particular concern are the grandfathering provisions. While some form of grandfathering might be a reasonable approach to addressing the hundreds of high-or moderate-risk LDTs that were developed under the existing regulatory system, the provision needs to be appropriately structured to minimize risk and to allow the FDA to evaluate these tests when necessary. For example, when a developer modifies a grandfathered test in a way that would effectively create a new test, this should trigger FDA review. The FDA should also have broad authority to request data about the performance of a grandfathered test if it has reason to be concerned about that test's validity. These postmarket authorities are essential to ensuring that unreliable tests are not permitted to remain on the market by virtue of when they were developed. However, in the current draft, it is not clear that these conditions are met. Furthermore, VALID exempts from premarket review all tests that are on the market up to the day of enactment of the legislation. This is a change from previous versions of the legislation, which exempted tests from review if they were on the market 90 days prior to enactment. This change in the grandfathering date would allow a greater number of tests onto the market without FDA review, and would only encourage developers to flood the market with tests in the final window before the legislation is enacted.

In addition to grandfathered tests, the legislation includes exemptions for certain categories of new tests, some of which are defined very broadly. For example, tests defined as low risk would be exempt from premarket review, much as they are now, and would only need to be registered with the agency before coming to market. However, low-risk tests are defined so broadly in VALID that it could potentially capture a significant amount of tests that the FDA would previously have considered to be moderate risk, and therefore needing review before being used with patients.

The exemption for "instrument families" raises similar concerns. Instruments—also known as platforms—are designed to run multiple different tests for many different purposes. A product flaw or other performance issue in an instrument can thus affect the validity of hundreds of tests. The current exemption for instrument families would allow a developer to obtain premarket approval for a single instrument which would then apply to other versions of that instrument, both previous and subsequent, that share certain core features. While some updates and modifications to instruments may not need premarket review from the agency, the current

[4] D. Lim, "FDA Reverses Policy That Let over 100 Antibody Tests on Market without Review," POLITICO, May 4, 2020, https://www.politico.com/news/2020/05/04/fda-enacts-stricter-rules-for-antibody-tests-after-congressional-investigation-233867.

exemption is constructed broadly and could allow for modifications that may impact an instrument's validity—all without agency review.

We are also concerned about certain provisions governing the review of modifications to IVCTs, particularly for those tests that are broadly exempted from premarket review. Unlike the current standard under the 510(k) pathway—which requires agency review of modifications that "could affect" device performance—VALID only enables the FDA to review modifications that impact analytical or clinical validity. This could pose challenges for enforcement, as it relies on developers to make this determination. Given the bill's extensive exemption categories, it will be critical that the FDA is aware of and has the ability to review any modifications that *might* affect analytical or clinical validity, whether or not such an effect is intended by the developer.

Other exemption categories in VALID may require additional consideration to ensure that they are appropriately risk-based and serve public health interests. We have provided comments to that end in the enclosed copy of the legislation.

The Value of Technology Certification Remains Untested and Unclear

As we noted in previous comments, technology certification (which was previously referred to as precertification) attempts to provide an opportunity for regulators to ensure test quality with minimal resource expenditure, while also allowing flexibility for qualified test developers to modify or develop new tests without additional review.

However, this pathway represents a significant departure from the premarket process the FDA has traditionally used to ensure safety and efficacy, shifting much of the focus of FDA oversight to the postmarket context. The consequence of this shift is that test developers could legally market tests that have never come under direct FDA review, but which have received FDA authorization to be on the market. If the eligibility standards for technology certification are too low, patients will be put at risk.

Additionally, the scope of a single technology certification order is very broad. As currently defined, a developer could, for example, submit data on a single test that uses mass spectrometry and receive a certification that covers all of the mass-spectrometry tests that it develops. This could allow hundreds of tests to come to market without FDA review.

By the FDA's own estimates, 40% of tests on the market would be eligible for this pathway. Given the potential for a single certification order to cover a large number of tests, the legislative text in its current form does not provide enough certainty that the potential benefits of this approach outweigh the real risks to patients.

Additionally, the current version of VALID sets too low a bar for developer eligibility. As written, developers would only be disqualified if: 1) they have committed significant violations of section 353 of the Public Health Services Act within the last five years which have not been resolved or are not related to a test under the certification order; or 2) have submitted information to the FDA that is false or misleading about a certified or approved test, or which violates any certification requirements that expose people to serious risk. These standards would exclude only

the most irresponsible actors and are much less stringent than the criteria in previous versions of the bill. More is needed to ensure that only the highest quality developers would be trusted to produce new tests without premarket review and that the tests emerging through this pathway would meet the same standard as those subject to full premarket review.

We recognize that, even with the current technology certification provisions, the oversight proposed in VALID is more robust and risk-based with respect to laboratory-developed tests than under current law. It is important for patients that Congress reform oversight of clinical tests to institute a meaningful regulatory framework that provides regulatory clarity and better protects public health. In any regime, there will be resource constraints on the FDA, and technology certification has been proposed as a mechanism for efficient resource allocation. In the absence of significant additional agency funding, such a pathway may be a necessary step to creating a regulatory framework that brings all clinical tests into FDA purview. However, the technology certification provisions in VALID leave more questions than answers, and therefore the prudent approach would be to initially structure the program as a pilot, subject to evaluation, before imposing an untested system on such a large proportion of the diagnostics market.

FDA's Postmarket Authorities Must Be Strengthened to Ensure Safety

Postmarket surveillance, adverse event monitoring, and regular inspections are critical features of FDA oversight, and would be particularly important under the regulatory framework outlined in VALID. This is because, as noted above, VALID exempts several categories of tests from premarket review, and creates new expedited or otherwise abbreviated pathways to market for many other types of tests. By the FDA's estimate, only about 5-10% of tests would be required to go through premarket review. This would significantly shift the burden of regulatory oversight to the postmarket setting for nearly all in vitro clinical tests. Such an approach may be appropriate given the nature of these products, which can follow a more iterative development path and in some contexts are routinely modified to address new research findings or meet clinical needs. However, this approach only works if the FDA's postmarket authorities are adequate.

However, VALID imposes unnecessary restrictions on the FDA's ability to establish postmarket surveillance requirements, and does not do enough to ensure that regulators have access to the information they need to evaluate a test's performance or detect problems that may only emerge over time with greater utilization in a broader patient population.

Though imperfect, adverse event reports are an essential source of information about the real world performance of medical products. These data will provide regulators with insight into the effectiveness of mitigating measures, and more generally, whether current approaches toward matching regulatory requirements to the risks posed by tests are well-calibrated.

As currently written, VALID would grant the FDA valuable insight into the performance of LDTs and would shorten some timelines for reporting compared to current requirements for approved tests, but it would not improve adverse event reporting overall. Current regulations for IVDs require user facilities—namely health care providers that purchase and use these tests—to report adverse events. However, under VALID, only test developers are mandatory reporters,

and they are only required to report this information when events are not due to laboratory errors. These changes will result in fewer reports to the agency and an increased likelihood that such tests are unnecessarily putting patients at risk.

Furthermore, while care has rightly been taken in the legislation to eliminate confusing and costly jurisdictional overlap between the FDA and the Centers for Medicare & Medicaid Services (CMS), equal attention has not been paid toward ensuring that the FDA has access to information needed to effectively oversee the testing market. Because adverse event reporting requirements under CLIA are described by different regulations and structured in the service of different goals, such information may not currently be provided to CMS with the necessary details for the FDA to consider it actionable under its unique regulatory standards and public health mission. Furthermore, instead of providing a conduit for this information from CMS to FDA, or a Congressional mandate to the agencies to establish such a relationship, VALID simply eliminates those reporting requirements that may be addressed in part by laboratories' compliance with CLIA requirements. This does not serve public health and should be reconsidered.

Finally, one of the most important postmarket tools in VALID is the Special Rule. In previous versions of the legislation, we were pleased to see its inclusion, as it provides the FDA with the statutory authority and the flexibility to act when it becomes aware of a test that may pose a risk to public health. Changes in the introduced version of VALID compromise this invaluable tool, and unnecessarily put the onus on FDA to demonstrate—with statutorily defined valid scientific evidence—that there is insufficient evidence to support the validity of a test. The FDA must also demonstrate that the test is being offered by the developer with deceptive or fraudulent claims, or that it is reasonably possible that the test will cause a serious adverse event. This is a much higher bar compared to other FDA-regulated products. Indeed, it is not clear how the agency could assemble evidence showing that there is insufficient evidence of something.

By raising the bar in this way, VALID will tie regulators' hands and prevent the agency from conducting the kind of nimble oversight that a risk-based and flexible regulatory framework requires. Going forward, it is imperative that the Special Rule revert back to previously drafted versions that do not tie the agency's hands.

FDA must have resources in order to implement and enforce this law

As noted previously, Pew appreciates Congressional efforts to align the regulation of the diagnostics market with the risk posed to patients, and believe the FDA is best situated to provide this oversight under a uniform regulatory pathway for all IVCTs. But it simply cannot do so without the resources to support these efforts.

The work of implementing VALID and carrying out its numerous mandates requires funding beyond what is currently provided to the agency as part of its baseline appropriations. However, the bill does not authorize new Congressional appropriations, and requires the agency to issue certain regulatory guidances before it can collect any user fees. Guidance development requires resources, as well as sufficient time to allow for public input. This process can take years. Given

the delayed authorization of a user fee program and the lack of supplemental appropriations authorized in the bill, the FDA's implementation of VALID's provisions may be compromised.

While there may be reason to debate the merits of funding such a system through user fees, Congressional appropriations, or some combination thereof, it is more important that there be certainty that these resources will be provided. Without these resources, the agency will be unable to fully implement the legislation as Congress intended, and will fail to grant the regulatory certainty that the VALID Act importantly seeks to provide.

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Pew appreciates this opportunity to comment on your efforts to modernize the oversight of diagnostic tests. Should you have any questions, or if we can provide any assistance, please do not hesitate to contact Elise Ackley at eackley@pewtrusts.org or (202) 540-6464.

Sincerely,

Elizabeth Richardson, MSc.
Project Director, Health Care Products