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The Honorable Patty Murray,
Chair
Committee on Health, Education,
Labor and Pensions
United States Senate
428 Dirksen Senate Office Building
Washington, DC 20510

The Honorable Richard Burr,
Ranking Member
Committee on Health, Education,
Labor and Pensions
United States Senate
833 Hart Senate Office Building
Washington, DC 20510

Dear Senators Murray and Burr:

Thank you for your continued efforts to streamline the regulation of clinical testing through the Verifying Accurate Leading-edge IVCT Development (VALID) Act, as included in the discussion draft of the Committee's user fee reauthorization package. 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).

We thank the committee leadership for their ongoing efforts to move this bill forward and we appreciate the opportunity to provide further input on this important topic. We also understand the significant amount of effort and careful negotiation that was required to arrive at the current version of the discussion draft.

However, while some of the changes proposed in the discussion draft would better protect patients from substandard *in vitro* clinical tests (IVCTs), several important provisions discussed below could undermine FDA's ability to oversee this diverse and rapidly growing market if not structured appropriately.

We acknowledge that key sections of the bill remain in brackets pending final resolution of these outstanding items, and we are hopeful that the Committee will be open to input from patient and public health groups like Pew as it considers changes to the discussion draft. We firmly believe that the time to create a flexible, risk-based regulatory system for all IVDs is now, and we remain committed to working with you and the committee to advance the legislation.

As you continue to refine the legislation, we strongly urge you to consider the following recommendations, all of which are more fully described in our redline of the discussion draft:

1. **Exemptions:** The legislation exempts broad categories of tests from premarket review, some of which need to be narrowed in order to ensure that high-risk tests are subject to the appropriate oversight. Additionally, certain key exemption categories contain bracketed language that must be retained in order to ensure those tests will be required to meet the statutory standard for analytical and clinical validity.

2. **Technology certification**: Though we remain concerned that this novel approach could be implemented safely on such a wide scale, and continue to believe that piloting the idea would be the most prudent approach, we believe that a review pathway like technology certification could, if appropriately structured, allow developers more flexibility to modify or develop new tests without undermining public health. However, it is vital that currently bracketed language be retained to make clear that new tests introduced under an approved technology certification order would be required to meet the applicable standard for validity and quality, and that FDA would have the authority to set clear guardrails for how developers could qualify for technology certification that covers multiple technologies.

3. **Postmarket oversight**: Given the proportion of tests that would be exempt from premarket review under the VALID legislation, FDA's postmarket authorities need to be sufficient to allow the agency to know how tests are performing and take action when necessary to protect public health. However, VALID does not provide FDA with the tools that it needs to do this. In particular, the FDA's authority under the Special Rule must be strengthened, and its ability to access information about the validity of tests on the market must not be hampered.

4. **Resources:** The legislation must provide adequate resources for the FDA to effectively implement these reforms and 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. It also limits how those user fees could be applied in a way that would seriously undermine the agency's ability to implement the legislation.

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. If appropriately structured, such a framework would 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, many of which raise concerns. If they are not carefully defined, categorical exemptions from review can lead to serious risks.

In general, such exemptions should only be applied in cases where the costs associated with premarket review outweigh the benefits to public health. Thus, exempting low-risk, custom, or low-volume tests makes 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 would undermine public health.

Legacy Tests

Of particular concern are the provisions related to tests that are on the market prior to VALID's enactment. While some form of exemption for legacy tests—or "grandfathered" tests, as they are

referred to in the bill—might be a reasonable approach to addressing the thousands 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 legacy test in a way that could affect its analytical or clinical validity, this modification should trigger FDA review—the current version of the bill would not require such an approach. The bill also contains several bracketed sections related to legacy tests that must be retained in order to ensure that FDA can require corrective action or withdraw a test that does not meet the applicable standard. We have provided more detailed recommendations on which language should be retained in our redline.

Much like any other test on the market, legacy tests should also be subject to ongoing FDA monitoring. We recognize that developers may not have data available for their legacy tests that conforms to current FDA requirements, and we agree that oversight of these tests should not unnecessarily burden developers. However, it is imperative that FDA can access the data it needs to evaluate the validity and quality of any test, particularly those it has never reviewed. If tests that have been on the market for several years are truly safe, accurate, and reliable, then developers should have data on hand to demonstrate this fact, which could be readily shared with the agency. They should also be able to report basic performance data through the Comprehensive Test Information System, just like any other test that is on the market.

Humanitarian Test Exemption
In addition to legacy tests, the legislation includes exemptions for certain categories of new tests, some of which are defined very broadly. For example, under the humanitarian test exemption, the bill would exempt any test that is used to diagnose a disease or condition with 10,000 or less cases in the United States per year. Unlike previous versions of the bill, this exemption does not establish other requirements related to the severity of the disease or a lack of alternative testing options. Given that the risk of a test is not linked to how many people have a condition, but rather how many people will receive a potentially inaccurate results from it, we believe that additional criteria should be included in this exemption to ensure that it does not become a loophole for risky, unreliable tests. The current language that is included in brackets would exclude screening tests and tests for contagious diseases from the category, and we believe it is essential that this language is retained.

Low, Moderate, and High-risk Tests
While we appreciate that the current draft now includes a moderate risk category, the definition provided for these tests needs to be refined to ensure that it does not leave regulatory gaps or overlap with the definition for high-risk tests. Similarly, the definition for high-risk tests is very narrow, and should be broadened to ensure that tests considered high risk under the current framework continue to be consider high risk under VALID. We believe that the definition of low-risk is now well-defined and appreciate your changes to this provision.

Modifications
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. Given the bill's extensive exemption categories, it is critical that FDA is able to review modifications that would affect the analytical or clinical validity of a test, or change the performance claims that a

developer makes about it. It is also important that a modified test be held to the applicable standard. For this reason, we urge you to retain the bracketed language currently in the bill.

Other exemption categories in VALID may require additional consideration to ensure that they are appropriately risk-based and serve public health interests.

Technology Certification

As we noted in previous comments, technology certification 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.

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. By the FDA's previous estimates, 40% of tests on the market would be eligible for this pathway. Given the potential for a single technology certification order (TCO) to cover hundreds 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.

Scope
The scope of a single TCO 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-based tests that it develops, provided those tests are not high-risk. This could allow hundreds of tests to come to market without FDA review. However, whereas the previous version of VALID limited the scope of an order to a single technology, the current draft would allow an order to apply to multiple technologies. We recognize that some labs routinely use certain technologies in combination in order to run particular tests. However, it is essential that FDA be allowed to carefully define through guidance or regulations the circumstances in which a developer could receive an order that covers more than one technology. We urge you to retain the bracketed language that stipulates this requirement.

Review and Approval
Furthermore, while previous versions of VALID would require developers to renew their technology certification order on a regular basis, this requirement has now been removed, which means that FDA would not have the authority to review any new test introduced under a given TCO, even if that test were for a completely different clinical specialty or context of use. This is particularly concerning given that under the current draft, it is not clear that FDA could take action to require a correction or remove a test that does not meet the applicable standard, as the language that would authorize them to do so is in brackets.

Eligibility
The criteria that a developer would have to meet in order to be eligible for technology certification also raise concerns. 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 two years which have not been resolved; or 2) have submitted information to the FDA that is false or misleading about a certified or approved test, or violated any VALID Act provisions that expose people to serious risk. These standards would exclude only the most irresponsible actors. Given the significant percentage of tests that will qualify for this pathway, 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, 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 need to be clarified and in some cases amended in order to ensure that patients and public health are not put at risk.

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 previous 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 agency has comprehensive information about the performance of tests on the market and can take meaningful action to protect patients and public health when a test poses an unacceptable risk.

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.

Ensuring Transparency

As noted above, FDA's ability to know what tests are on the market is particularly important given the number of tests that will be exempt from premarket review. Particularly for legacy tests, which number in the thousands, it is critical that FDA know how they are performing and what claims are being made about their reliability and accuracy. While we applaud the requirement that nearly all tests be registered in the Comprehensive Test Information System, the bill does not require legacy tests to submit performance claims to CTIS. Additionally, the bill includes bracketed text that would require the developers of those tests to maintain documentation that the test continues to meet exemption criteria and to present this documentation to FDA upon request. We strongly urge you to retain this bracketed language.

Postmarket Surveillance
FDA uses postmarket surveillance studies to help better understand how a test is performing in the real world, and its ability to require these studies is an important postmarket authority. However, under the current draft the FDA would only be able to require such a study if the failure of the *in vitro* clinical test to meet the applicable standard is reasonably likely to result in serious adverse health consequences or death. It is highly unlikely that the FDA would ever approve a test that is likely to result in death—this standard is more appropriate for banning a test from the marketplace. We strongly urge you to revise this language to bring it in line with current drug and device provisions governing postmarket surveillance.

Special Rule
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 take action when it becomes aware of a legacy test that may pose a risk to public health. Changes in the introduced version of VALID compromised this invaluable tool, and unnecessarily put the onus on FDA to demonstrate that there is insufficient evidence to support a determination of test validity. While the language in the discussion draft represents an improvement, the bar is still far too high, and would be largely unworkable for the agency. It is also not clear that legacy tests would need to meet the applicable standard under this provision.

Reform Will Fail Without Adequate Resources for FDA

As noted previously, Pew appreciates Congressional efforts to align the regulation of the diagnostics market with the risk posed to patients, and believes 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 any comprehensive reform to diagnostics oversight will require funding beyond what is currently provided to the agency as part of its baseline appropriations. However, VALID continues to provide no path forward for how the agency will do this, as it does not authorize new Congressional appropriations, limits the application of user fees to premarket review activities, and does not authorize FDA to collect those fees until after it has developed certain regulatory guidance. 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 would likely 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 necessary reforms and will fail to grant the regulatory certainty that test developers require.

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Though the issues described above would need to be satisfactorily resolved in order to assure stakeholders that FDA has the authority it needs to effectively regulate diagnostic testing, we remain optimistic that this could be accomplished in a way that ensures patients are better protected under VALID's regulatory framework. Pew sincerely appreciates this opportunity to comment on your efforts to modernize the oversight of diagnostic tests and we are happy to answer any questions about our comments or redline draft (attached). Should you have any questions, or if we can provide any assistance, please do not hesitate to contact Kyle Kinner at kkinner@pewtrusts.org pr (202) 540-6597

Sincerely,

Elizabeth Richardson, MSc.
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