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August 23, 2021

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 Michael Bennet
U.S. Senate
Washington, DC 20510

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

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

Thank you for your continued efforts to streamline the regulation of clinical testing through the reintroduction of 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).

We thank the sponsors for their ongoing efforts to move this bill forward and appreciate the opportunity to provide further input on this important topic. We are also encouraged by the recent Department of Health and Human Services' (HHS) technical assistance (TA) recommendations in response to the bill, which made clear that diagnostics reform is a priority for this administration. Pew is in alignment with them on several key issues related to VALID. We are optimistic that your offices and the Department will continue to work with the broader stakeholder community to modernize the current fragmented oversight system.

Fundamentally, and consistent with sentiments noted in the HHS TA, we feel strongly that the current version of the bill fails to strike the right balance between enabling rapid market entry and ensuring patient safety. Though some of the changes would better protect patients from substandard *in vitro* clinical tests (IVCTs), most appear to favor rapid market access over patient safety. Given this fact, we are concerned that the legislation would not constitute an improvement on the status quo. Though we have optimistically monitored the legislative discussions on this issue over the last several years, and Pew greatly appreciated the opportunity to provide comments at several stages, we think this version of the bill represents a step backwards in achieving the regulatory balance needed to ensure an effective risk-based framework.

That said, we remain committed to working with you and the committees to advance legislation that brings all *in vitro* diagnostic tests—including those developed and used in individual laboratories—under one risk-based regulatory system.

As you continue to refine the legislation, we strongly 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 must 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 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, many of which raise concerns. If not structured appropriately, categorical exemptions from review can lead to serious risks. The COVID-19 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 be marketed without receiving an Emergency Use Authorization.¹ Within weeks, the agency had to reverse course, after receiving numerous reports of unreliable serology tests for sale.² This example 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

¹ <https://www.fda.gov/news-events/fda-voices/insight-fdas-revised-policy-antibody-tests-prioritizing-access-and-accuracy>

² <https://www.politico.com/news/2020/05/04/fda-enacts-strict-rules-for-antibody-tests-after-congressional-investigation-233867>

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.

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 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 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.

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—a suggestion that was also included in the HHS TA.

Furthermore, VALID still exempts from premarket review all tests that are on the market up to the day of enactment of the legislation. This cut-off date would only encourage developers to flood the market with tests in the final window before the legislation is enacted. The prior discussion drafts of VALID set the cut-off date for all legacy tests at 90 days prior to enactment, which we believe was a more reasonable timeframe. Additionally, the current version of VALID does not require legacy tests to submit an annual report to FDA—a change from previous versions that further reduces the agency's insight into how these tests perform. Postmarket authorities, such as annual reports, are essential to ensuring that unreliable tests are not permitted to remain on the market by virtue of when they were developed.

Low-risk Tests

In addition to legacy tests, the legislation includes exemptions for certain categories of new tests, some of which are defined very broadly. For example, low-risk tests 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, the current definition of low-risk tests is so broad that it could potentially capture a significant number of tests that the FDA would previously have considered to be moderate- or high-risk, and therefore needing review before being used with patients. We strongly concur with HHS's proposed change to the definition of low-risk as well as the clear articulation of the moderate-risk category, which achieves the goal of creating regulatory clarity, and reduces the risk of up- or down-classification.

High-risk Tests

Similarly, changes to the definition of high-risk tests exclude more tests from this designation. Given that there is no defined moderate-risk category in the bill, this would push even more tests into the low-risk category. The definition proposed in the HHS TA is a more appropriate approach to defining test risk.

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. Unlike the current standard under the 510(k) pathway—which requires agency review of modifications that “could affect” device performance—VALID only enables 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 is critical that FDA be aware of and have 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.

The Value of Technology Certification Remains Untested and Unclear

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 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.

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 tests that it develops, provided those tests are not high-risk. Given the changes to the definition of a high-risk test, this could allow hundreds of tests to come to market without FDA review. Furthermore, the current version now allows tests brought to market under a technology certification order to remain “cleared” and legally marketed even if the technology certification order expires, raising quality control issues. If a developer decides to let their certification order expire, then the bill should allow products under that order to remain on the market only if the agency has directly reviewed them.

Similarly concerning is the new language stating that if a developer modifies a test under a TCO in order to address a potential risk to public health, FDA does not need to approve the change either before or after it is made, even if that change would place the test outside the scope of the original TCO. If a developer makes such a significant modification to a test, they should seek approval from FDA within some specific timeframe.

Eligibility

We appreciate the changes in the introduced bill that suggest a distinction between tests “approved” via premarket review and those “cleared” via a TCO, as well as the changes to developer eligibility for the pathway. However, the bar is still set too low. 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 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. 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.

Representative Tests

Additionally, representative tests submitted as part of a technology certification application must now be of ‘appropriate complexity’ (rather than the highest complexity, as before) but it is not clear what criteria would be applied to determine the appropriate level of test complexity, nor is it clear to what standard such tests would be required to meet. Previously, representative tests were required to meet the applicable standard for approval—i.e., analytically and clinically valid. Now, representative tests would be required to meet the “applicable standard for such order,” which does not appear to refer to the applicable standard defined in the legislation, but rather some other, not clearly defined standard that is specific to a technology certification application.

While we support this effort to distinguish between cleared and approved tests, it is imperative that all tests on the market be analytically and clinically valid for their intended use, even if they have not been reviewed by the agency. This is why we appreciate HHS’ changes to the applicable standard [See 587A (a)(1)(D)], which would make clear that regardless of a test’s pathway to market, it must be both analytically and clinically valid and supported by valid scientific evidence.

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 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 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 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.

Adverse Event Reporting

Though imperfect, adverse event reports are an essential source of information about the real world performance of medical products. As noted in the HHS TA, adverse event reporting is a key tool for mitigating risk and ensuring patient safety. 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. Both of these changes will result in fewer reports to the agency and an increased likelihood that such tests are unnecessarily putting patients at risk.

Overlap with Clinical Laboratory Improvement Amendments (CLIA)

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 CLIA reporting requirements are described by different regulations and structured in the service of different goals, this information may not include 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.

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 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.

Notably, the HHS TA proposed removing the Special Rule and adding provisions throughout the bill that would significantly strengthen the agency's ability to request documentation from a developer about their exempt tests. This change could have the effect of making the agency's postmarket authorities more flexible, durable, and resistant to legal challenge. We strongly prefer this approach and urge you to take this proposal into consideration. As currently constructed, the Special Rule will tie regulators' hands and prevent the agency from conducting the kind of nimble oversight that a risk-based and flexible regulatory framework requires.

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, and requires the agency to issue certain regulatory guidance 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 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 preclude Pew's support of the legislation in its current form, we remain optimistic that changes could be made so that patients are better protected under VALID's regulatory framework compared to the current system of oversight. Pew sincerely appreciates this opportunity to comment on your efforts to modernize the oversight of diagnostic tests and we hope to provide further assistance to your offices in addressing these concerns. 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,

A handwritten signature in black ink, appearing to read "Elizabeth Richardson", is centered below the word "Sincerely,".

Elizabeth Richardson, MSc.
Project Director, Health Care Products