THE PEW CHARITABLE TRUSTS

2005 Market Street, Suite 2800 215.575.9050 Phone
Philadelphia, PA 19103-7077

901 E Street NW 202.552.2000 Phone
Washington, DC 20004
www.pewtrusts.org

February 15, 2019

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

Re: VALID Act Discussion Draft

Dear Representatives DeGette and Bucshon and Senator Bennet:

The Pew Charitable Trusts is pleased to offer comments on the Verifying Accurate Leading-edge IVCT Development (VALID) Act discussion draft. Pew is an independent, nonpartisan research and policy organization with a longstanding focus on the quality and safety of medical products, and our work includes research and policy analysis on issues related to the regulation of *in vitro* diagnostics (IVDs).

As noted in Pew's comments to the Food and Drug Administration (FDA)'s technical assistance to the Diagnostic Accuracy and Innovation Act (DAIA)[1], the current system of regulation for *in vitro* diagnostics has failed to adapt along with technological advances in the industry and changes in providers' use of such tests. Because patients should be able to trust the results of clinical tests, no matter where they are developed or performed, Pew appreciates your efforts to reassess this regulatory framework and to develop a reform proposal that attempts to balance the need for ongoing innovation in this field with the need to protect patients from potential harms.

Areas of agreement with Pew's principles for reform

In our previous comments, we proposed a series of principles that should guide any evidence-based approach to reform in this area. We are glad to see that these principles are broadly reflected in the VALID Act. VALID integrates portions of DAIA with several important concepts contained within the FDA TA, creating a regulatory framework that addresses many of the stakeholder concerns over the current regulatory structure which have impacted patient care.

[1] See "Pew Comment Letter on FDA's Response to Diagnostic Accuracy and Innovation Act." Available at: 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.

Regulatory requirements should be primarily driven by risk

VALID brings all *in vitro* tests under a common regulatory framework—though, notably, several categories of tests are exempted from certain new requirements—while providing flexibility for developers to bring tests to market through several different pathways.

Unlike the current regulatory system, where only some IVDs are subject to risk-based FDA oversight—this approach creates a regime that would regulate tests based on the risk they pose to patients, not where they are developed and performed.

Access to information about tests and their performance

The draft legislation provides regulators with significantly more information about tests currently in use and their performance. Unlike the current environment, in which FDA enforcement discretion regarding laboratory-developed tests leaves the agency with little insight into a large portion of the market for clinical tests, VALID would require test developers to register with the FDA. The FDA would also receive more robust information about test performance as developers are required to report adverse events to the FDA (promptly for serious adverse events and quarterly for others) and to submit certain descriptive and performance information to the Comprehensive Test Information System (CTIS). Adequately funding CTIS will ensure that it is a meaningful resource for both the FDA and the public at large.

These provisions will provide essential information for regulators and the public on the full range of marketed tests and their performance, allowing the FDA to recognize trends and identify problematic tests more quickly, and enabling health care providers to make more informed decisions about use.

Ensuring adequate and clear enforcement authority over all tests

The draft legislation grants the agency new enforcement authorities that would allow for prompt action when problems arise. This includes the ability to recall problematic tests, regardless of whether they are exempt, precertified, or subject to premarket review. The FDA could also request additional information and even raw data from test developers and require developers to establish mitigating measures that can help to reduce the risks associated with a given test.

As it establishes these new authorities, VALID also attempts to more clearly define jurisdictional lines between the FDA and the Centers for Medicare & Medicaid Services (CMS), which would help to eliminate unnecessary duplication of effort or conflicting regulatory requirements. Clear division of regulatory authority and lines of accountability will also help to strengthen oversight and streamline enforcement of the bill's provisions.

Tests would be held to a more appropriate and meaningful standard.

VALID would replace the current standard applied to diagnostics—the medical device standard of reasonable assurance of safety and effectiveness—with an evaluation of a test's clinical and analytical validity. These are key standards that should be applied to all clinical tests. Patients and providers must be able to trust that a test accurately detects or measures the substance being measured (analytical validity), and that the information provided adequately relates to the specific condition being diagnosed or treated (clinical validity). Clinical tests are an important source of information for health care providers and are often used to guide consequential treatment decisions. So, the accuracy and reliability of these tests is essential.

Areas of concern

Though the draft is largely consistent with the principles for regulatory reform that Pew has outlined previously, there are several areas that are concerning or unclear.

Precertification attempts to address an important need, but its utility remains questionable

We applaud the FDA and VALID's authors for embracing novel ways to reform IVD regulation, including the consideration of the new concept of precertification. By allowing certain developers to bring to market a group of tests based on the review of one representative test, regulators may be able to ensure test quality with minimal resource expenditure. Such a pathway could help to allocate regulatory resources where they are most necessary.

However, if a precertification pathway is implemented, it would also mark a significant change to the current FDA approval paradigm, shifting much of the focus of FDA oversight for these tests from premarket review 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 precertification are too low, patients will be put at risk.

The primary advantages of this novel approach are more efficient allocation of limited regulatory resources and faster market access for developers; however, it is essential that the benefit to patients should outweigh the risk of fewer tests being subject to direct FDA review. This will require careful balancing to ensure that on the one hand, the eligibility criteria are narrow enough and other oversight mechanisms are strong enough to ensure that only high-quality developers receive precertification, while at the same time eligibility criteria are broad enough to attract these developers to the program.

Although precertification could present a relatively efficient way of providing more oversight to the LDT market than is currently conducted under the FDA's policy of enforcement discretion, we are concerned that the legislative text in its current form does not provide certainty that the potential benefits of precertification outweigh the risk. For example, it remains unclear what protocols, policies, and experience a developer would be required to demonstrate in order for the FDA to grant a precertification application. Furthermore, inspection is not described as a

mandatory requirement prior to approval of an application, suggesting that it may be envisioned solely as a postmarket mechanism. These are essential aspects of evaluating the potential risk and benefit and an essential gatekeeping mechanism to restrict eligibility and protect patients.

Given our concerns about this novel approach, we appreciate that the scope of the certification itself, and the scope of tests eligible for precertification, are both relatively narrow. Unlike FDA's proposed digital pre-certification pilot, which is a firm-level certification, the precertification proposed here is tied to a group of tests with certain shared attributes, and not to the firm or test developer. It requires submission of data regarding a representative test from each test group, which would give the FDA greater insight into and, importantly, control over the tests that come to market through this pathway.

Furthermore, pre-certification appears to be available to a relatively narrow range of tests. Neither high- nor low-risk tests are eligible, leaving only those tests that would fall into what is effectively a "moderate-risk" category—high-risk tests with mitigating measures—as eligible for the pathway. Even then, large portions of the testing market are excluded, including "first-of-a-kind" tests, test systems for home use, "cross-referenced" tests, and direct-to-consumer (DTC) tests. FDA has the authority in the VALID proposal to expand the tests eligible for precertification, but the initial narrow scope is appropriate to ensure that the pathway is more established before it is expanded to additional types of tests. In fact, Congress may want to consider initially introducing precertification as a pilot program, which could be expanded and made permanent over time if the benefits of the precertification pathway are demonstrated to outweigh the risks of permitting tests to come to market without prior FDA review.

We recognize that, even with the precertification 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 protects public health. In any regime, there will be resource constraints on FDA, and precertification has been proposed as a mechanism for efficient resource allocation. In the absence of significant additional agency funding, precertification may be a necessary component to creating a regulatory framework that brings all clinical tests into FDA purview. However, if an insufficient volume of tests come to market through this pathway, the precertification pathway will not function as intended. As the precertification proposal is revised to better ensure that benefits outweigh risks, it will be important to ensure that it will nevertheless draw enough developers to prevent implementation of VALID from being cost-prohibitive or undesirably slow.

Inadequate adverse event reporting will compromise FDA oversight

By bringing all clinical test developers into the adverse event reporting system, VALID provides new and important information to regulators on adverse events. It also shortens some timelines for reporting, as compared to current requirements for approved tests.

However, the scope of reportable adverse events is concerningly narrow. Under the current draft, an adverse event would only be reportable if it both caused or contributed to death or serious injury *and* is the result of a malfunction, and even then, is not reportable if it was attributed to

laboratory error. It is important to recognize that many user errors relate to the design of the underlying user interface. Furthermore, VALID narrows the scope of required reporters, excluding user facilities that perform tests that have not been modified (who are required to report adverse events under current law). Limiting adverse event reporting in these ways excludes a significant and meaningful set of information that would allow the FDA to exercise effective oversight of the entire market for clinical tests. More complete post-market information is necessary for the FDA to protect patients.

Regulatory reform will fail to make an impact without adequate FDA resources

The VALID Act enumerates many new regulatory requirements and proposes new regulatory functions. In order to perform these functions, the FDA will need adequate resources. However, under the current draft of the legislation, it is not clear that these needs will be met.

A new user fee program to support these functions will likely be essential. However, the imposition of new costs could have an adverse effect on smaller-scale test developers, such as academic labs. While the structure of these user fees should not pose insurmountable barriers to market entry, it is important that funding for this regime is adequate—this may require a combination of user fees and Congressional appropriations.

Extensive use of third party organizations

VALID proposes to use third-party organizations to carry out a range of regulatory functions, including inspections, premarket review of new tests, risk categorization, and important review roles under the precertification pathway. The use of third-party organizations to serve key functions has some precedent—for example, medical device inspections and application review—and could improve efficiency by leveraging existing sources of expertise within the IVD industry. Given the nature of this reform—which proposes to bring significantly more tests under some form of agency review—the use of these outside resources may be necessary, particularly while FDA gains additional experience with these products and works to grow its staff of technical experts.

However, simply contracting out this work may not provide for sufficient performance and lower costs. In the last year, FDA has issued a plan designed to prevent the agency's re-review of medical devices reviewed by accredited organizations,[2] while the Centers for Medicare & Medicaid Services has issued a request for information in regard to potential conflicts of interest posed by those Accrediting Organizations (AOs) that provide both accreditation and consulting services to providers participating in the Medicare program.[3]

---

[2] "Eliminating Routine FDA Re-Review of Third Party 510(k) Reviews." Available at: https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/Third-ParyReview/UCM620308.pdf

[3] "Medicare Program: Accrediting Organizations Conflict of Interest and Consulting Services; Request for Information." Available at: https://www.federalregister.gov/documents/2018/12/20/2018-27506/medicare-program-accrediting-organizations-conflict-of-interest-and-consulting-services-request-for

Taking this experience into account, more mechanisms can be built into the legislation to ensure that accreditation serves the public interest. This could include mandatory annual audits and accompanying reports to Congress or providing for revocation of accreditation when those audits or postmarket monitoring mechanisms reveal that invalid tests have come to market as a result of a substandard precertification inspection or premarket application review.

It may also include affirmative criteria that must be considered when reviewing an accreditation application, such as demonstrated subject matter expertise in a particular diagnostic area or technology. These mechanisms may be established by directing the Secretary to issue regulations or directly via statute.

More clarity needed

We appreciate the opportunity to provide analysis before all of the details have been resolved. Though the VALID Act provides more detail around certain mechanisms compared to both DAIA and the FDA's technical assistance to that draft, areas of ambiguity remain and significant provisions of the draft are in brackets, including those outlining the precertification pathway, accredited persons, the Comprehensive Test Information System, and user fees. Recognizing that crafting effective legislation of this type requires a careful balance and cannot provide complete certainty, the risk-benefit profile of the reform will change as vaguely defined and bracketed provisions are fleshed out. We look forward to sharing our analysis as these details emerge.

As Congress works to fill in details regarding aspects of the VALID proposal, it is important to recognize that the current framework requires reform because it has failed to keep pace with changes in technology and clinical practice. In finalizing this legislation, Congress should set clear and appropriate expectations, but allow reasonable flexibility for the regulator to ensure that implementation can adapt to future changes in technology.

* * *

Given the growing range and complexity of *in vitro* tests, as well as their importance in guiding key treatment decisions, oversight is important to ensuring test accuracy and validity and, ultimately, to protecting patients. 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

CC: Chairwoman Anna Eshoo, Ranking Member Michael C. Burgess, M.D., Chairman Frank Pallone, Jr., Ranking Member Greg Walden, Chairman Lamar Alexander, Ranking Member Patty Murray