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AdvaMedDx: Key Areas for Discussion Regarding VALID Act Draft

AdvaMedDx appreciated the opportunity to provide comments to the House Energy & Commerce Committee on the VALID Act draft legislation, and to review the technical assistance (TA) on the legislation provided by FDA. AdvaMedDx supports the process being undertaken by the Committee, and appreciates the Congressional commitment to advancing a framework for in vitro diagnostics tailored to their use in healthcare today, and that will provide for regulation of the full range of clinical diagnostic tests under a unified approach, regardless of where a test is developed.

Based on our review of FDA's TA and discussions with stakeholders, this document identifies and summarizes some of the key areas of the VALID Act that would benefit from further discussion among stakeholders. Each of these aspects of in vitro clinical test (IVCT) regulation is critical to ensuring that the resulting legislation is fully understood and will deliver on Congress's goal to provide an appropriate, forward-looking paradigm for the regulation of in vitro clinical tests. This document does not repeat the specific suggestions we made in response to the Committee's request for comments, but does explain some of the core areas of uncertainty that motivated our comments.

Risk-Based Classification and Oversight:

AdvaMedDx seeks to ensure that the resulting review paradigm for IVCTs represents a risk-based approach that serves the public health by calibrating oversight based on the test's intended use. This will allow FDA's review resources to focus on higher risk tests, regardless of source, and is consistent with Congressional directives in the 21st Century Cures Act and the underlying concept of a least burdensome approach.

The VALID Act largely adheres to this risk-based principle in categorizing tests that would be: (1) registered and listed with FDA, but not subject to premarket review; (2) subject to an abbreviated premarket application; or, (3) subject to a full premarket application. The draft legislation also specifies the elements of review for abbreviated and full applications. (Alternatively, eligible IVCTs have the option to seek marketing authorization through the voluntary precertification program). However, in some instances, test types are summarily subject to a level of review that is misaligned with the level of risk of such test type. In other cases, tests may be subject to requirements without consideration of the use of the test intended by its sponsor. More broadly, some of the elements and concepts used to determine the pathway

to market lack a common understanding among stakeholders, or could be applied in a manner that is not least burdensome. Finally, it is unclear how FDA would apply some of the application review elements described in the draft.

While FDA has indicated that the agency expects that a relatively high proportion of IVCTs would ultimately be exempt from premarket review, stakeholders are concerned that the current draft of the legislation could end up being applied in such a manner that many tests currently exempt from review would suddenly be subject to review—and many tests currently subject to 510(k) clearance could end up with a "PMA-like" application under the new system—without any change to the risk level of the respective tests.

Below we have highlighted some specific examples:

- [*Give a concrete example of a test type, such as a home use test that is low risk and pretty well understood; why should that be subject to a full review?*]
- [*Describe concern with ambiguity of the "well-characterized" concept; and concerns with notification elements*]
- [*Give salient examples of currently exempt tests that risk being subject to review under the new system, and of currently 510(k) tests that would appear to be subject to full review under the new system*.]

Test Platforms:

Perhaps the primary example of a departure from a consistent risk-based approach is the draft's treatment of test "platforms" (e.g., sequencers, readers, spectrometers). Many test platforms are currently exempt from premarket review or cleared via 510(k), because the platforms themselves are typically intended for a limited purpose or intended use by their developer or because they are for general use rather than use with a specific test. However, these platforms may also be leveraged by a more advanced type of assay, and end up being reviewed as part of the submission of that higher-risk assay.

For example, a sequencer is used to determine DNA base pairs. For that general purpose, it is generally subject to 510(k) clearance. If the sequencer is then used by the sponsor of a next generation sequencing test to identify particular biomarkers that function as a companion diagnostic for a particular cancer treatment, the sequencer may be further reviewed under a PMA for that more specific, and higher-risk, intended use.

Under the draft, all platforms would be subject to premarket review, without regard to their intended use and whether they are subsequently used by a more advanced assay such as a next generation sequencing companion diagnostic. FDA acknowledges that platforms are intrinsically lower risk particularly when for general use, but the agency argues for premarket review of all platforms via an abbreviated review assessing the platform's analytical validity. The agency has also indicated support for legislative language clarifying that developers may submit concurrent submissions for platforms and IVCTs, leveraging the same data sets as applicable. Absent

incorporation of a platform into an IVCT for a particular clinical use, however, it is unclear exactly how FDA contemplates conducting its review of a standalone platform, as the precise applications of the platform would not be known. The sponsor of a platform would potentially be compelled to partner with the maker of a more advanced assay in order to obtain an FDA approval, which may inhibit development and impede market access for platform sponsors.

- [*Example of a platform currently exempt that would be regulated under VALID.*]
- [*Example of platform that would have a tough time going through a review on its own and how its sponsor would be impeded in terms of having to find a partner that would run an assay on that platform*.]

Modifications to Approved IVCTs:

Although the VALID Act contemplates that numerous test types would qualify for the precertification pathway, many test types would be required to obtain approval through a traditional application process; in other instances, sponsors of precertification-eligible tests will nevertheless opt to obtain traditional approval. As is true of the current device review paradigm, it is essential to define what types of modifications of an approved IVCT will require a new application and approval before being implemented. In the comments submitted by AdvaMedDX, we suggested several clarifications to ensure that a change within the scope of an approval, or in accordance with an approved change protocol, is not considered a modification that requires supplemental review and approval before marketing.

More broadly, some of the core concepts in the VALID Act that will be critical to determining whether a modification requires a new approval are novel, such as test notification elements; these concepts sometimes replace more familiar concepts, such as intended use. As a result, there is significant uncertainty as to how modifications would be evaluated in practice, and stakeholders have limited ability to predict how modifications for IVCTs would be treated under the VALID Act compared to the current modifications standards for clearance or approval of devices.

- [*During the meeting, participants mentioned performance changes, notification elements, and adding genes to a panel for germline tests. We should provide several concrete examples of a change that should NOT trigger a new submission (but might under the current language), or a change for which the implications are simply unclear. Preferably, these should be examples for tests that would be subject to approval in the first instance, rather than exempt or pre-cert eligible, such as a change to a high risk test or first of a kind test*.]

Precertification for IVCTs:

The VALID Act embraces the concept championed by FDA that many types of innovative diagnostics can be more effectively regulated through a precertification of the developer and its

test validation process. Under this approach, which FDA describes as necessary to the feasibility of this new regulatory framework, the agency would evaluate IVCT developers and their process for developing certain tests, to ensure that current and future iterations of such tests developed under the terms of their precertification will be analytically and clinically valid. AdvaMedDx strongly supports the concept of precertification for IVCTs as part of any diagnostics reform framework.

As we have expressed in our comments, we believe it is important that the precertification program allow sufficient statutory flexibility—both with regard to what types of tests can apply, and what is included in the submission—so that it will stand the test of time as technologies continue to evolve and our understanding of innovative test types matures. Towards that end, we are concerned about the statutory disqualification of many test types. Although there is a mechanism for FDA to revisit these statutory disqualifications, that process seems likely to be cumbersome, and many of the disqualified test types are either already well understood or are rapidly becoming better established and characterized. Instead, test developers should generally have the ability to demonstrate that a test is appropriate for precertification, and FDA should have the discretion to consider that, on a case by case basis.

For the same reasons, the scope and process for granting a precertification should not be so cumbersome as to detract from its use for those test types for which it is envisioned. An ineffective precertification program will result in more individual test applications than FDA has indicated it can reasonably review. We agree with FDA's suggestion that the precertification of a test can cover multiple medical specialties when appropriately validated and supported in the precertification submission. Nevertheless, other aspects of the scope of precertification and review of precertification submissions remain unclear or have the potential to be too restrictive for the program to succeed.

- [*Provide examples of a home use, DTC, and/or first of a kind test that should easily be reviewable via precertification.*]
- [*Provide example or question to pressure-test how the medical specialties would work in practice*.]
- [*Provide example demonstrating that the notification elements are too restrictive and that the scope of a precert should be more flexible.*]
- [*Provide example regarding the representative test; any key questions about the nature of the demonstration of a clinical program and validation?*]